Universidade de Aveiro
Ano 2016

Departamento de Ciências Médicas

NÁDIA FILIPA CRUZ LOURENÇO

ESTÁGIO CURRICULAR NUMA UNIDADE DE FARMACOLOGIA CLÍNICA

CURRICULAR INTERNSHIP IN A CLINICAL PHARMACOLOGY UNIT

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Relatório de estágio curricular apresentado à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Biomedicina Farmacêutica, realizado sob a orientação científica do Professor Doutor Joaquim José Coutinho Ferreira, Professor Associado da Faculdade de Medicina da Universidade de Lisboa, e do Professor Doutor Bruno Miguel Alves Fernandes do Gago, Professor Auxiliar Convidado do Departamento de Ciências Médicas da Universidade de Aveiro

Dedico este trabalho aos meus pais, Elisabete e Fernando, pelo esforço que fizeram para me proporcionar todas as oportunidades durante todos estes anos.

o júri

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palavras-chave ensaios clínicos, gestão de dados, *medical writing*, farmacovigilância, investigação clínica

resumo

O presente relatório de estágio descreve a experiência adquirida durante o estágio curricular realizado na Unidade de Farmacologia Clínica (CPU) do *Instituto de Medicina Molecular (IMM).* Esta unidade é constituída por diferentes unidades de trabalho, o que me permitiu estagiar em diferentes atividades relacionadas com o âmbito deste mestrado, como a coordenação de ensaios clínicos, farmacovigilância, revisões sistemáticas, gestão de dados e *medical writing*. Este relatório, para além da descrição das atividades desenvolvidas, descreve o estado da arte da investigação clínica e alguns aspetos relativos à Farmacovigilância.

O estágio realizou-se de 14 de Setembro de 2015 até 30 de Junho de 2016. Este estágio teve como objetivo pôr em prática os conhecimentos obtidos durante a formação académica, adquirida principalmente durante o primeiro ano do mestrado, e aprofundar esses conhecimentos numa vertente prática. Durante este estágio, foi possível observar e compreender as dificuldades práticas e logísticas da condução de ensaios clínicos e outros projetos de investigação num centro de investigação. Foi também possível observar o funcionamento de uma unidade de Farmacovigilância e de uma unidade de Bioestatística/Gestão de Dados. Para além disso, este estágio, como primeiro contacto com o mundo do trabalho, foi uma oportunidade para melhorar algumas competências e capacidades sendo por isso uma excelente experiência profissional e pessoal.

Keywords clinical trials, data management, medical writing, pharmacovigilance, clinical research

abstract

The present internship report describes the acquired experience during the curricular internship performed at the Clinical Pharmacology Unit (CPU) of the *Instituto de Medicina Molecular (IMM).* This unit is comprised by different work units, which allowed me to perform different activities related with this master, such as clinical trials coordination, pharmacovigilance, systematic reviews, data management and medical writing. This report, besides the description of the developed activities, describes the state of the art of clinical research and some aspects of pharmacovigilance.

The internship took place from 14th September 2015 to 30th June 2016. This internship intended to put into practice the knowledge acquired during the academic training, mainly those acquired during the first year of master's degree, and to deepen this knowledge in a practical manner. During this internship, it was possible to observe and understand the practical and logistical difficulties that a research unit faces during the conduction of clinical studies and other types of research projects. It was also possible to observe closely the functioning of a pharmacovigilance unit and a biostatistics/data management unit. Additionally, this internship, as the first contact with the professional world, was an opportunity to improve some competences and skills and was an excellent professional and personal experience.

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Abbreviations

AD – Alzheimer ’s disease

ADR - Adverse Drug Reaction

BC - Before Christ

CAML – Centro Académico de Medicina de Lisboa

CEIC – Comissão de Ética para a Investigação Clínica

CNPD – Comissão Nacional de Proteção de Dados

CPU - Clinical Pharmacology Unit

CRF - Case Report Form

DSUR - Development Safety Update Report

EC – European Commission

ECG - Electrocardiogram

eCRF – Case Report Form

EDSS - Expanded Disability Status Scale

EMA - European Medicines Agency

EU – European Union

FAP - Familial Amyloid Polyneuropathy

FCT - Fundação para a Ciência e Tecnologia

FDA - Food and Drug Administration

FMUL - Faculdade de Medicina da Universidade de Lisboa

GCP - Good Clinical Practice

GDP - Gross Domestic Product

GMP - Good Manufacturing Practices

GVP - Good Pharmacovigilance Practices

HD - Huntington’s disease

HSM-CHLN - Hospital Santa Maria – Centro Hospitalar Lisboa Norte

ICH - International Conference on Harmonisation

IMM - Instituto de Medicina Molecular

INFARMED - Autoridade Nacional do Medicamento e Produtos de Saúde I.P.

IVRS - Interactive Voice Response System

IWRS - Interactive Web Response System

LCPT - Laboratory of Clinical Pharmacology and Therapeutics

MAA - Market Authorization Application

MedDRA - Medical Terminology for Drug Regulatory Authorities

MRI – Magnetic Resonance Imaging

MS- Multiple Sclerosis

NDA - New Drug Application

NICE - National Institute for Health and Care Excellence

NPS - National Pharmacovigilance System

PD – Parkinson's Disease

QMS - Quality Management System

SIV - Site Initiation Visit

SPC - Summary of Product Characteristics

SUSAR - Suspected Unexpected Serious Adverse Reaction

SVIG - National Pharmacovigilance System Database

UFLVT – Unidade de Farmacovigilância de Lisboa e Vale do Tejo

UK - United Kingdom

UKCRC - UK Clinical Research Collaboration

USA - United States of America

WHO - World Health Organization

WMA - World Medical Association

1. Introduction

The present document is a report where I describe my curricular internship carried out as an integrant part of the second year of the Master's degree in Pharmaceutical Biomedicine of the University of Aveiro. The purpose of this internship was to provide on-the-job training that allowed me to put into practice the concepts and competences gained during the masters.

This on-job-experience was conducted under the supervision of Professor Joaquim Ferreira and Professor Bruno Gago at the Clinical Pharmacology Unit (CPU) of *Instituto de Medicina Molecular* (IMM) from September 2015 until June 2016. During this experience, I had the opportunity to be in touch with several areas such as clinical trials of neurological disorders (on the Clinical Trials Subunit), pharmacovigilance (at the Safety and Drug Utilization Research Subunit) and data management and medical writing (at the Biostatistics and Methodological Subunit and at the Outcome Research Subunit). The possibility of working in different areas was the main reason why I choose IMM to make my curricular internship.

At the beginning of my training and taking into account the characteristics of the host institution were defined some objectives and learning outcomes. These objectives were:

- To acquire skills in clinical research coordination and perform the daily activities as a study coordinator of a clinical research centre;
- To gain knowledge about all the processes and issues involved in clinical trials, and the experience and skills that are required of all the different professionals working on clinical trials;
- To acquire basic knowledge about the application of statistical methods in research projects occurring in the CPU;
- To participate in research projects and develop methodologies to plan and conduct a project;
- To improve the knowledge and skills in pharmacovigilance and acquire qualifications to perform daily activities of a regional pharmacovigilance unit;
- To identify potential areas of professional interest within the clinical research and pharmaceutical industry fields;
- To develop and improve my personal, interpersonal and professional skills in an interdisciplinary environment, such as communication, organization, critical thinking, problem solving, autonomy and responsibility.

This internship gave me the chance to achieve these objectives and learning outcomes. Thus, I was able to consolidate and improve my knowledge in the mentioned areas in a real work environment. This on-job-experience, as the first contact with the real work environment, offered me the possibility to learn in a variety of situations, and contributed significantly to my personal and professional growth.

I structured this report in order to allow a better understanding of the hosting institution and the activities that I worked in, presented in the next sections. I start by given an overview of the IMM's structure, with a focus on research unit where I worked.

To better contextualize my internship I also present a discussion on the state of the art of clinical research (subchapter 1.2), alongside a brief description of clinical trials, their regulatory framework, their current state in the world, and the current landscape of clinical trials in Portugal. Owing to the myriad of activities I conducted throughout my internship, I also briefly touch upon pharmacovigilance, data management and medical writing activities.

Following this introductory chapter, I begin dwelling in more practical aspects of my internship in chapter two, which is divided in two subchapters. The first subchapter deals with general training that I had the opportunity to attend. The second subchapter discusses specific training I was required to undertake to successful carry my activities in the host institution.

Chapter 3 gives an in-depth look at the challenges, experiences and achievements during this internship and how they help me achieve the learning outcomes I set out at the beginning of my internship.

Chapter 4 is the final chapter, and concludes the present document.

1.1. Structure of the Host Institution

As previously mentioned, the curricular internship was performed in the CPU of the IMM. Looking to provide an overview of the host institution, this suchapter describes the activities performed by IMM, its goals and structure. The host institution is included in a consortium that integrates IMM, Santa Maria Hospital (HSM-CHLN – *Hospital de Santa Maria - Centro Hospitalar Lisboa Norte*) and Faculty of Medicine of the University of Lisbon (FMUL- *Faculdade de Medicina da Universidade de Lisboa*). This consortium was created in 2009 by the Ordinance nº1371/2009 and is called *Centro Académico de Medicina de Lisboa* (CAML) (1).

The main goal of IMM is to promote and encourage research and in fact, IMM is already considered one of the main Portuguese biomedical institutions with a wide range of international recognition.

IMM is composed by several preclinical and clinical research units covering a relevant part of biomedical research (2). During my curricular internship I worked in a clinical laboratory, the Joaquim Ferreira Lab. The current subchapter will provide a look at this research unit.

1.1.1. Instituto de Medicina Molecular

The IMM is a research institute associated to the Portuguese Ministry of Science and Higher Education and is located in the campus of the FMUL and HSM-CHLN. IMM has established itself as a biomedical research laboratory conducting rigorous and innovative basic, clinical and translational biomedical research with the mission of improving human life through a better understanding of disease mechanisms, development of new predictive tests, improvement of diagnostic tools and development of new therapeutic interventions. IMM was founded in December 2002 as result of the association of 5 previous research units from the FMUL: the Biology and Molecular Pathology Centre, the Lisbon Neurosciences Centre, the Microcirculation and Vascular Pathobiology Centre, the Gastroenterology Centre and the Nutrition and Metabolism Centre.

The institute is a private and nonprofit association, and is essentially supported by national public funds and European Union (EU) funds. Over the last years, IMM was capable of establishing several prestigious international collaborations and start-up companies, and displays a high profile of international grants (2).

Considering the IMM's Activity Report of 2014, IMM spent a total of € 13.920.579 in research. Important parts of expenditures were supported by *Fundação para a Ciência e Tecnologia* (FCT) grants and other national and international grants. In 2014, IMM had 331 research grants ongoing. One of the most interesting aspects about the research grants in 2014 was the large increase of the number of private national research grants to 147 grants against the 114 FCT grants (2). Moreover,

other international institutions and European Commission (EC) grants maintain a positive tendency of investment.

Furthermore, the scientific productivity of the institute has seen a major growth since its foundation, in both quantity and quality. In 2014, IMM had 193 publications on international journals (29 publications were published in journals with an impact factor higher than 10) and made 286 communications in international conferences (2).

1.1.2. Clinical Pharmacology Unit (Joaquim Ferreira Lab)

The CPU or Joaquim Ferreira Lab is one of the IMM's research laboratories and is physically located in the Laboratory of Clinical Pharmacology and Therapeutics (LCPT) on the third floor of the HSM-CHLN, in Lisbon.

The central aim of the CPU is to contribute to the development of effective and safe therapeutic interventions through the creation of optimized methodologies for the design, conduction, analysis and report of clinical trials (3).

The Joaquim Ferreira Lab was formally created on the 1st of July 2013, with members of the research team from the Neuropharmacology Unit of the Neurological Clinical Research Unit and the members of the Laboratory of Clinical Pharmacology (FMUL). Funding for the unit is mainly guaranteed by international research grants (3).

In 2015, the CPU researchers published 49 publications in scientific journals, made 23 communications in international conferences and participated on 71 advanced training events (2).

The current structure of CPU comprises distinct functional subunits which are described in the next paragraphs.

1.1.2.1. Clinical Trials Subunit

The Clinical Trials Subunit is located on the sixth floor of the Neurology Department of the HSM-CHLN and was created in 1999. Its work activities include the conducting of clinical and observational studies of medicines in Parkinson's disease (PD), Huntington's disease (HD), Alzheimer's disease (AD), Familial Amyloid Polyneuropathy (FAP), Multiple Sclerosis (MS) and other movement disorders.

The hospital has a long history with neurology clinical trials, with more than a hundred of studies performed since its foundation. The pivotal clinical trials for Levodopa, the current gold standard for the treatment of PD, were conducted in the Neurology Department of HSM-CHLN.

Currently, the subunit has more than 15 ongoing clinical trials sponsored by the pharmaceutical industry and a sizeable number of observational studies, some of which investigator trials.

1.1.2.2. Biostatistics and Methodological Subunit

The Biostatistics and Methodological Subunit was established in order to support all research projects developed by the CPU, such as the design, conduction, statistical analysis and reporting of clinical research studies. Some of the main activities of this team include sample size calculation and generation of randomization lists for the collaborators' studies.

1.1.2.3. Outcomes Research Unit

This subunit of the CPU is focused on the study of outcome measurement instruments, including biomarkers and patient reported outcomes in intervention evaluation. In other words, this subunit is concerned with the study of outcomes and their prognosis following the use of a therapy.

1.1.2.4. Safety and Drug Utilization Research Subunit

The Pharmacovigilance Unit of Lisbon and Vale do Tejo (UFLVT – *Unidade de Farmacovigilância de Lisboa e Vale do Tejo*), one of the regional units of the decentralized National Pharmacovigilance System (NPS), is responsible for handling pharmacovigilance duties. This regional unit covers more than 3,6 million inhabitants and is the second biggest unit of the Portuguese pharmacovigilance system. It plays a key role in the development of research projects on drug utilization and safety and its main activities include the reception, classification, processing and validation of spontaneous adverse drug reactions reports. An adverse drug reaction (ADR) is a noxious and unintended response to a medicine and it can be reported by spontaneous reporting method which is an unsolicited communication by a healthcare professional or consumer to a company, regulatory authority or to other organization that describes one or more ADRs in a patient who was given one or more medicinal products and that does not derive from a study (4,5).

The Safety and Drug Utilization Subunit is also responsible for promoting the safe and rational use of medicines, in collaboration with the Portuguese medicines authority (INFARMED – *Autoridade Nacional do Medicamento e Produtos de Saúde I.P.*), and issuing pharmacovigilance training to health professionals and the general population.

1.1.2.5. Drug Evaluation and Systematic Reviews Subunit

This subunit integrates the Portuguese Branch of the Iberoamerican Cochrane network and the Movement Disorders Cochrane Collaboration Review Group.

This subunit focuses on conducting systematic reviews, allowing the development of databases with updated, concise and reviewed medical information. A systematic review is defined as *"a review of the evidence on a clearly formulated question that uses systematic and explicit methods*

to identify, select and critically appraise relevant primary research, and to extract and analyse data from studies that are included in the review"(6). These reviews and databases are very useful to support the decisions of health professionals, patients and health authorities.

1.1.2.6. Pharmaco-Magnetic Resonance Imaging Subunit

This is a small subunit whose the main purpose is the development of projects on the imaging area, through magnetic resonance imaging (MRI) and detection of biomarkers related with the progression of PD.

1.2. State of the Art

This subchapter provides a background about the main areas involved in the on-the-job training: clinical trials, pharmacovigilance, data management and medical writing.

The first part is about clinical research, starting with a brief introduction on clinical research, mainly clinical trials, and the regulatory framework of clinical trials in Europe and in Portugal. The current state of clinical trials in the world and particularly in Portugal is also mentioned. In this section, I present data from some European countries (that can be comparable in some characteristics with Portugal) and their measures to increase the number of clinical trials.

The pharmacovigilance part includes a short description of the historic evolution of pharmacovigilance up to the current pharmacovigilance systems, the pharmacovigilance legislation in Europe and Portugal and an explanation about the Portuguese pharmacovigilance system.

The last part of this subchapter is about data management and medical writing, where some general concepts are presented.

As my internship was mostly concerned with clinical trials, the state of the art subchapter will focus on this topic.

1.2.1. Clinical Research

1.2.1.1. Clinical research and its historic evolution

According to the new Portuguese law, clinical research can be defined as any systematic study conducted in humans or with individual clinical data, to investigate or verify the distribution or the effect of health factors, health states or results, disease or health processes and/or to verify the safety of interventions or health services, through biological, behavioral, social or organizational aspects (7). Therefore, clinical research can be divided into two large groups: the observational studies and clinical trials.

Observational studies or non-interventional studies involve the direct observation of individuals in their natural setting without a direct intervention by the evaluator except the collection of data. In observational studies, researchers do not have any influence on the progress of events, and only collect the relevant data (7,8).

Clinical trials aim to have some influence on the healthcare provided to the patient in order to determine the efficacy and safety of one intervention (7,8). However, clinical trials do not tell all we need to know about the use of one medicine. Then, once the drug is marketed, it is important to try to evaluate the patient's response on routine medical practice (7,8).

The advancement of clinical research crosses an extensive journey and goes back to the biblical narrative in 500 BC (Before Christ) in which a military leader ordered his soldiers to eat only meat and drink only wine, a diet he believed would keep them in a good physical condition. However, some young soldiers followed a vegetarian diet of vegetables and water for 10 days. When the experiment ended, the second group appeared better nourished than the first one.

Over the years, the experiments have evolved and controlled trials grew in complexity. The famous 1747 scurvy trial conducted by James Lind contained most elements of a controlled trial. The Scottish physician Lind was confronted by the high mortality of scurvy amongst the sailors whilst working as a surgeon on the naval ship Salisbury. Thus, he planned a comparative trial with 12 ill sailors who were divided into 2 groups, with all subjects showing similar symptoms. Isolated from the rest of the group, the men were given the same supplies, but each pair was allocated to a different scurvy treatment: either cider or oranges and lemons. The results were clear: the use of oranges and lemons had the best results.

Another milestone was the arrival of placebo in 1863 in a clinical trial conducted by Austin Flint to treat rheumatism. The first double blinded trial was done in 1943 to investigate the patulin treatment for common cold. Three years later the idea of randomization was introduced in a clinical trial to study streptomycin in pulmonary tuberculosis (9).

The history of clinical research covers a wide variety of scientific, ethical and regulatory challenges. The ethical advances in human protection include several milestones – the Nuremberg Code, the Universal Declaration of Human Rights, the Declaration of Helsinki, the Belmont Report and the International Conference on Harmonization Good Clinical Practices guidance. In parallel to the ethical guidelines, clinical trials started to become progressively more regulated. This evolution of ethical guidelines and regulatory framework was made simultaneously with the history of abuses and accidents over the years with the intention of avoid these situations and then promote the safety of clinical research participants (9). I will talk about these ethical and regulatory frameworks later.

1.2.1.2. Clinical trials and marketing authorization

The development of a new medicine includes an extensive process of investigation which starts with laboratorial and non-clinical investigations to verify if the drug is acceptably safe for the next step, the clinical trials.

A clinical trial is an intrinsic part of the development of new medicines. Clinical trials can be defined as any research study that prospectively assigns human participants to one or more health-related interventions to evaluate its effects on health outcomes. Indeed, when a new product is being studied, it is not completely known if it will be helpful, harmful or no different than the available ones (including no intervention) and if the new drug is effective. Thus, it is imperative to

determine the safety and efficacy of the intervention by measuring certain outcomes in human participants. Interventions include but are not restricted to drugs, cells and other biological products, surgical procedures, radiological procedures, devices, behavioral treatments, process-of-care changes, preventive care, etc (10). Some clinical trials compare interventions that are already available to each other.

The patient population must meet the predefined inclusion criteria to ensure a homogeneous population to facilitate the proper evaluation of clinical trial results and to protect participants' safety.

Most clinical trials are controlled, randomized and double-blinded studies. Clinical trials may compare a new medical approach to a standard one that is already available, to a placebo that contains no active ingredients, or to no intervention. The comparison between the investigational medicine and a control is important to have a better control over a study. This kind of study is called a controlled trial. In a randomized trial the participants are arbitrarily allocated to receive the experimental therapy, placebo or another therapy. The randomization has numerous advantages, including the elimination of bias of selection and allocation of participants, the facilitation of blinding and the maximization of statistical power. A blinded study decreases the risk of bias in the results by omitting the information about the medicine that the patient is receiving. Blinding can be either single-blinded, if the patient does not know in what study arm he is in, and double-blinded if both, patient and investigator, are unaware of the treatment.

Clinical trials follow a specific study plan, called a protocol, which is developed by the researcher or manufacturer and evaluated by the concerned regulatory authorities to obtain all the approvals and authorizations needed.

Generally, clinical trials are sponsored by pharmaceutical companies but academic centers, doctors or other health care providers and other organizations can also sponsor clinical studies. Usually, the clinical studies sponsored by industry are multicentre and multinational (performed in different centers and different countries, respectively) (11,12).

The clinical development one of a new investigational medicine involves different phases:

- **Phase I (Human Pharmacology Trials)**

Phase I trials, also known as the first-in-man studies, are initial safety studies whose aim is to establish the dose range tolerated by healthy volunteers for single and for multiple doses. Thus, these phase trials assess safety, tolerability, and the pharmacokinetic and pharmacodynamic profile of a new medicine. When it is ethically unacceptable to make these trials in healthy persons the trials are conducted in ill patients (e.g. oncology). Note that, these phase trials can also be conducted with very sick patients for whom treatment options are lacking.

Usually, Human Pharmacology Trials involve a small number of participants (6 -10 volunteers) (12).

- **Phase II (Therapeutic Exploratory Trials)**

Phase II trials are performed on larger groups of patients (20-300 depending on the type of disease). The aim of Therapeutic Exploratory Trials is to evaluate the therapeutic efficacy and safety of the medicine in patients affected by the disease that is currently in study. Phase II studies also provide data to decide what therapeutic regimens will be used in the next steps, with the selection of participants following very strict criteria (12,13).

- **Phase III (Therapeutic Confirmatory Trials)**

Phase III studies are carried out on large patient groups (300-3000 patients) across multiple study locations in order to confirm benefit, efficacy and safety and to determine how the new medicine is best prescribed to patients in the future. Usually, the new investigational drug is compared with other available treatments/placebo and can be tested in combination with other therapies. These Therapeutic Confirmatory Trials are often randomized and double-blinded. Phase III trials provide the primary basis for the benefit-risk assessment and much of the core information about the drug for inclusion in final labeling if approved by the regulatory authorities (12).

Following all of these phases, the sponsor makes an application to obtain a market authorization. In Europe there are several routes for the authorization of medicinal products: the centralized procedure (which is compulsory for some products and it is made directly to the European Medicines Agency (EMA), the mutual recognition procedure (based on the principle of recognition of an already existing national marketing authorization by one or more member states), the decentralized procedure (in which the application for the marketing authorization for one product is submitted simultaneously in several member states) and the national authorizations (where products are to be marketed in one member state only) (14). Normally, in Europe, the Market Authorization Application (MAA) is filled with EMA because the granting of a European authorization is binding in all member states. In the United States of America (USA), the New Drug Application (NDA) is filed with the United States Food and Drug Administration (FDA). A description of the manufacturing process along with quality data as well as preclinical and clinical trials' results is also needed to demonstrate the safety and efficacy of the new therapy (13).

- **Phase IV (Therapeutic Use Study)**

Phase IV studies, also known as Post-Marketing Surveillance Trials, are carried out after the medicine has received its market authorization. These studies are designed to provide broader efficacy/effectiveness and longer-term risks information about the already approved medicine, in large numbers of patients. These Therapeutic Use Studies involve thousands of participants and may continue for many years (12,13).

Until now the division of the clinical trials has been made according to four temporal phases (from phase I to IV). With this division, the type and design of studies performed in each phase were determined according to the results of previous phases. However, due to the evolution of the Research and Development paradigm and the evolution of clinical trials this concept is no longer accurate. In fact, the "*phase of development provides an inadequate basis for classification of clinical trials because one type of trial may occur in several phases"*(15). Thus, the classification through objective of study is preferable because it is more reliable (15).

1.2.1.3. The regulatory framework of clinical trials in Europe

Clinical research is an extremely regulated sector, with a series of laws, guidelines and ethical standards, in order to protect the rights and integrity of participants and to ensure a high quality of the data obtained.

The requirements to conduct clinical trials in Europe are established in the following documents:

- Declaration of Helsinki –a set of ethical principles published by the World Medical Association (WMA) to guide the protection of human participants in medical research. The first version was adopted by the 18th WMA General Assembly, Helsinki, Finland in June 1964. The declaration has been amended seven times, with the most recent version being adopted at WMA General Assembly in October 2013 (16).
- Nuremberg Code –a set of research ethics principles for human experimentation as a result of the atrocities that occurred during the Second World War by the Nazi regimen (17).
- Belmont Report – attempts to summarize the basic ethical principles identified by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (18).
- International Conference on Harmonisation (ICH) guidelines – The ICH is responsible for issuing recommendations to achieve greater harmonization in the interpretation and application of requirements related with the research and development of new human

medicines (19). Two important ICH guidelines for clinical research are the Good Clinical Practice (GCP) and Good Manufacturing Practices (GMP) guidelines. In Europe, these guidelines are also a legal obligation because they are required by the Clinical Trials Directive (the Directive 2001/20/EC) and both guidelines were transposed to European directives:

- Commission Directive 2005/28/EC of 8th April - lays down detailed guidelines for GCP in the conduct of clinical trials on medicinal products for human use in line with the principles referred in Directive 2001/20/EC (20).
- Commission Directive 2003/94/EC of 8th October 2003 – lays down the principles and guidelines of GMP in respect of medicinal and investigational products for human use. All manufacturers need an authorization to manufacture the investigational product as required by Directive 2001/20/EC (21).

- Directive 95/46/EC of the European Parliament and of the Council of 24th October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data (22).
- Regulation EU No. 536/2014 of the European Parliament and the Council of 16th April 2014 on clinical trials on medicinal products for human use which repeals the Directive 2001/20/EC, April 4th. This regulation applies to all clinical trials conducted in the EU but does not apply to non-interventional studies (23).

Note that all clinical trials performed in the EU are required to be conducted in accordance with Clinical Trials Directive (Directive 2001/20/EC) until the new Clinical Trials Regulation becomes applicable (23).

- Volume X of Eudralex - contains guidance documents applying to clinical trials.

➢ *From the 2001/20/EC Clinical Trials Directive to the current Clinical Trials Regulation*

Directive 2001/20/EC was extremely criticized due to its disharmonized interpretation which conducted to a dissimilar implementation of the directive in different member states and consequently to a decrease in efficiency of member states in clinical trials field. Indeed, the time and costs of conducting clinical trials in Europe grew significantly because:

- Staffing requirements for the clinical trial authorization process doubled;
- Insurance fees increased by 800 percent for industry sponsors;
- Administrative costs for non-commercial sponsors increased in 98 percent;
- Little cooperation among the member states.

All of these points conducted to a decrease in 25 percent on the number of clinical trial applications from 2007 to 2011 (24).

A “directive” is a legislative act that sets out a goal that all the EU countries must achieve. However, it is up to the individual countries to devise their own laws on how to reach these goals. By the other side, a “regulation” is a binding legislative act which must be applied in its entirety across the EU (25).

Therefore, new regulation (the Regulation EU No. 536/2014) was developed with the intention of making the EU more attractive for clinical trial research maintaining always the high standards of patient safety. One of the major preoccupations of this regulation is to simplify the submission of an application dossier for authorization and harmonize the procedures for conducting clinical trials. This new regulation will introduce a single submission dossier via a single EU portal to obtain the authorization to realize the clinical trial in different member states. This harmonized application dossier is composed of two parts:

- **Part I – Study specific documents**

This part integrates the scientific, therapeutic and safety aspects of the trial and should be assessed by the concerned member states in cooperation;

- **Part II – Country/site specific documents**

Includes documents / information related with biological samples, clinical trial agreements, informed consent and recruitment of subjects. These country specific documents will be assessed by each concerned member state. A national level body will review the documents as per the national applicable law but with one contact point and one fee per country (24).

Accordingly, certain aspects are not covered by the regulation and remain country specifics including ethics and other related topics. Consequently, additional approvals might still be required to realize a clinical trial (e.g. data protection in Portugal, radiation approval in Germany, etc.) (24).

In conclusion, the new regulation intends to facilitate the conduction of multinational clinical trials.

Moreover, the new regulation also includes more detailed safety provisions and new indemnity provisions. In regards to safety reporting, with the new regulation all Suspected Unexpected Serious Adverse Reaction (SUSAR) are required to be electronically reported by the sponsor directly into the Eudravigilance, instead of being submitted to each member state. Another important effort of this regulation is about transparency. Thus, clinical trials results will be made accessible in the European database and sponsors are subject to penalties if they fail this obligation (24).

1.2.1.4. The regulatory framework of clinical trials in Portugal

The conduction of clinical trials on medicines for human use in Portugal is governed by Law nº 21/2014 of 16th April which was already modified by Law nº73/2015 of 27 th July. The law itself is a transposition of Directive 2001/20/EC of the European Parliament and of the Council of 4th April, and partially implements Directive 2007/47/EC associated with clinical research on medical devices (26).

It is expected that the new Clinical Trials Regulation will not become fully applicable until 2017 due to the fact that the EU portal and database have to first be up and running. However, the new Portuguese law has already some of the main aspects of the new European regulation.

Other European directives were also transposed to the Portuguese law as is the case of Directive 2005/28/EC of 8th April which was transposed into national law by the Decree-Law 102/2007 of 2nd April, and Directive 95/46/EC of 24th October, concerning the protection of patient data which was transposed to the Portuguese law by Ordinance nº67/98 and by Resolution nº333/2007 (26).
In addition to the above legislation, there are a series of guidelines covering various matters related to clinical trials which are also applicable and can be found in Volume X of EudraLex.

In accordance with the Portuguese law for clinical research and as part of the harmonized European system, to conduct clinical trials in Portuguese research centers it is required an authorization from INFARMED, from the National Commission to Data Protection (CNPD – *Comissão Nacional de Protecção de Dados*) and a favorable prior opinion from the Clinical Research Ethics Committee (CEIC – *Comissão de Ética para a Investigação Clínica*) (26).

1.2.1.5. The current state of clinical trials in the world

ClinicalTrials.Gov, which is one of the biggest databases for clinical studies, lists 207847 studies with locations in all 50 states and in 191 countries, in February 2016. Interventional studies make up 80% of the registered studies with the remaining 39420 studies being observational studies. Furthermore, 38% of all studies registered in ClinicalTrials.Gov are just USA studies making the USA the republic with the highest number of clinical trials occurring (27). In Europe, Germany, France and the United Kingdom (UK) are the biggest players in clinical trials field (28).
Additionally, the number of clinical trials in Asia is increasing which shows the growing globalization of clinical trials (27).

The biggest players mentioned have economic and organizational conditions which are different from the Portuguese reality. As a result, I am going to talk about the UK as a reference European country; Austria due to the similar number of population; and Czech Republic due to the similar number of inhabitants and similar economic conditions.

- **The United Kingdom**

The UK is recognized as one of the most developed European countries in clinical trials field. Indeed, when searching for clinical trials conducted from January 2015 to December 2015 in the UK using the European database "Clinicaltrialsregister.eu", there are 819 EudraCT protocols registered with clinical trials occurring in this country (29).

The UK has implemented many policies and strategies in the clinical trials field that made the country very competitive in the field. For example, the UK has established an UK Clinical Research Collaboration (UKCRC) which is a partnership among the national health system, regulatory authorities, universities, research grants, pharmaceutical industries and patients associations to develop initiatives in order to improve clinical research. The UKCRC developed a set of standardized financial contracts for clinical trials to facilitate their implementation. Another important measure was the establishment of funds to support the investment in clinical research. Furthermore, the UK has made a significant effort to promote the involvement of the patients on the clinical research and to inform the community about its benefits. For that, the platform "People in Research" was created and the legal barriers of clinical trials advertisement were minimized. This was a very important measure to improve the recruitment rate which had been a major problem and continues a big problem in many other countries. The UK also created other platforms in which it's possible to design, conduct, manage the data and also analyze and publish clinical studies (28).

- **Austria**

Austria is one of the richest countries in the world and its population is about 8 623 073 inhabitants which is similar to the Portuguese population (10 562 178 inhabitants). In spite of having a similar number of inhabitants, Austria is a country with more clinical trials than Portugal. In 2015, 388 clinical trials were registered in the European database (29).

Some of the measures taken by Austria to improve clinical trials are similar with the already mentioned measures of the UK. In other words, web pages were created in order to facilitate patients' recruitment, creation of clinical research groups, distribution of funds to clinical research and training programmes to investigators (28).

- **Czech Republic**

The Czech Republic has a population of 10 541 466 and a Gross Domestic Product (GDP) per capita estimated for 2016 of $32 622, both similar to the Portuguese reality (30). However, Czech Republic had 371 clinical trials in last year, twice more than Portugal (29).

As other recognized countries, the Czech Republic has implemented important measures to improve its clinical trial competitiveness. In addition to some already mentioned measures in the other countries, it was also implemented payment to investigators for their investigational work which promotes a fair and effective way of payment for an additional work of the investigators (28).

1.2.1.6. The current state of clinical trials in Portugal

As shown by Figure 1, the number of submissions for clinical trials in Portugal between 2006 and 2012 decreased 26%, from 160 to 118 studies, with the lowest number of clinical trials ever submitted in Portugal being 2011, with only 88 studies. Since 2013 the number of clinical trials has been increasing with 137 clinical trials submitted in 2015, one year after the implementation of the new clinical research law. However, this number is still lower than in other countries of EU, as it is the case of the above mentioned countries (31). The rate of clinical trials per million inhabitants in Portugal is among the lowest in Western Europe (28).

When evaluating the process of clinical trial approval and consequently the competitiveness of Portugal, we see that the average approval time in INFARMED in 2015 was 28 calendar days which is an acceptable value and similar with competitive European countries (Figure 1) (31). INFARMED has been doing an effort to reduce this number over time. However, there are other entities such as the CNPD and the institution where the trial is to be conducted which did not have a legal deadline for approval of the financial contract and the aspects related with data protection. As a result, the time of approval of a clinic trial was in average 6 months which is not competitive with other countries. These particular aspects were addressed by Law nº21/2014 of 16th April, and it is expected a progressive increase in Portugal's competitiveness.

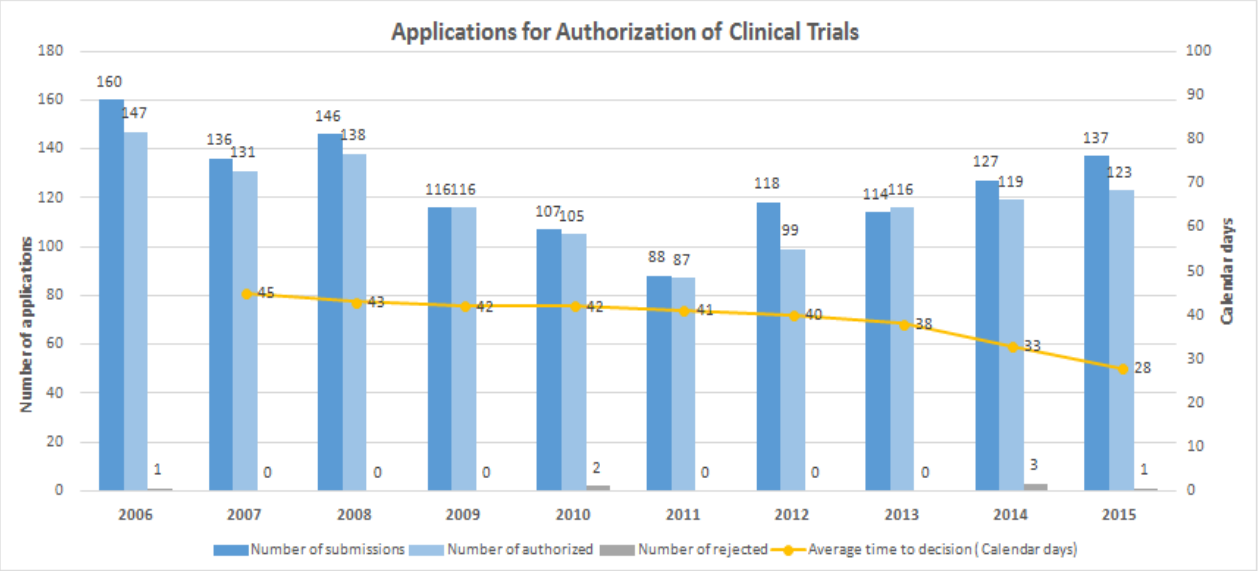

Figure 1 – Applications for authorization of clinical trials and average time to decision from 2006 to 2015 in Portugal. Adapted from (31).

Taking into consideration the number of clinical trials by phases (as represented in Figure 2) we can see that in Portugal, submitted applications for authorization of phase 3 trials make up 65.7% of all trials. Phase I clinical trials have almost no representation, with only 15 applications for authorization of phase I trials submitted in 2015 (31).

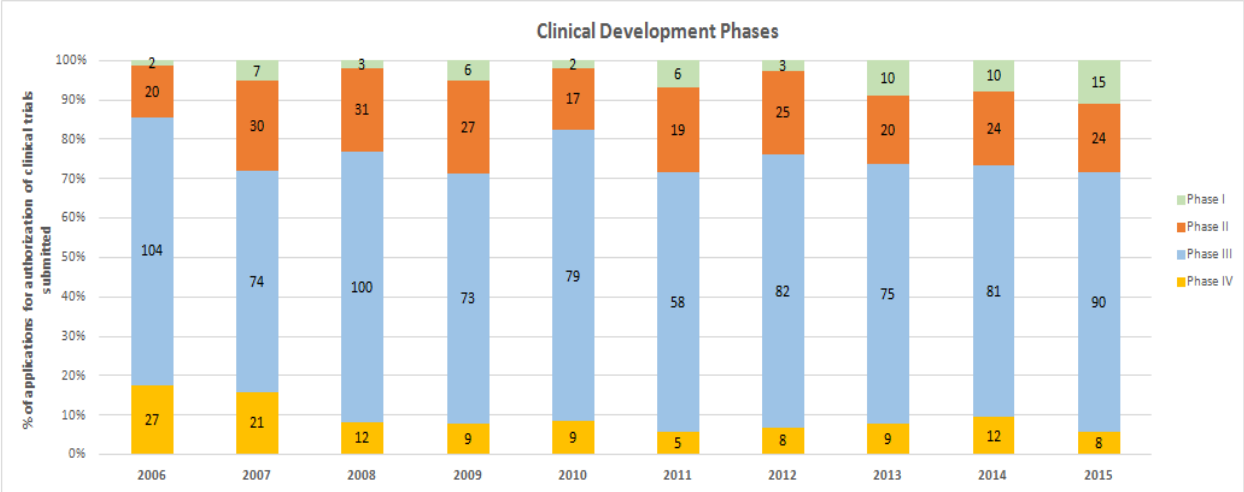

Figure 2 – Applications for authorization of clinical trials in Portugal by phases from 2006 to 2015. Adapted from (31).

Furthermore, clinical trials by initiative of investigator are also few, especially when compared with the UK and Spain, countries where academic clinical trials make up about a quarter of the total authorized trials in a year (28). In 2015, Portugal had only 13 applications for authorization of clinical trials by initiative of investigator (31). The highest number of applications for authorization of academic studies was reached in 2013 with 16 studies, a very low number. This demonstrates the lack of interest for clinical research in Portugal and the difficulties inherent to this activity. However, the new clinical research law has a number of measures to promote academic research, and these are expected to increase as a response.

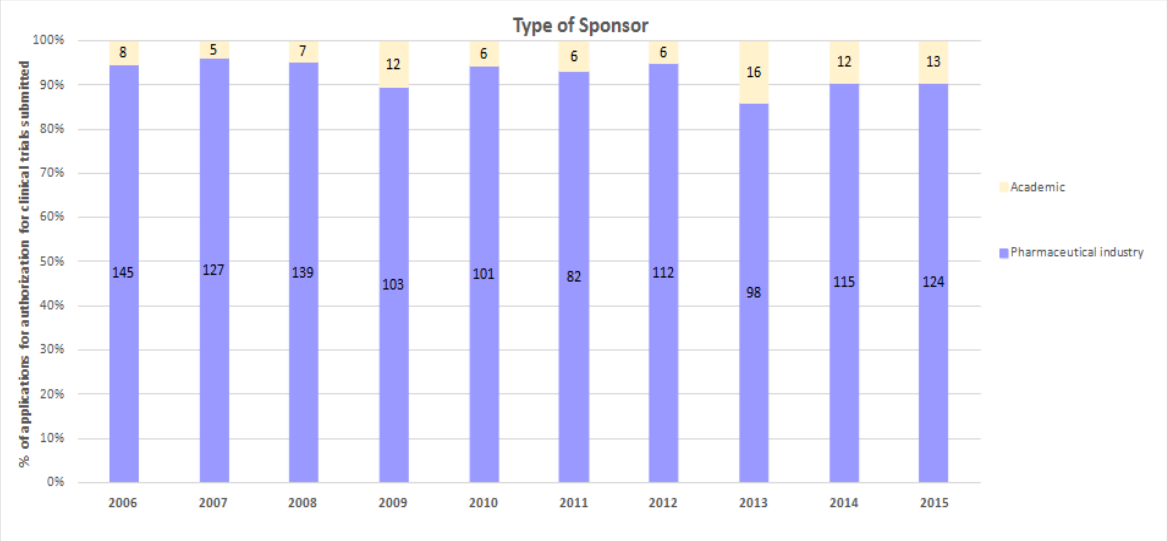

Figure 3 – Applications for authorization of clinical trials in Portugal by type of sponsor from 2006 to 2015. Adapted from (31).

Also the recruitment process in Portugal is an issue because Portuguese clinical centres recruit few participants and do not meet the established deadlines.

Considering the European countries mentioned above we can verify that the established measures were translated in a good increase of competitiveness in the clinical trials field. The number of clinical trials in Portugal was lower than Austria and Czech Republic (which are countries with similar number of inhabitants) probably due to the lack of incentives, organization, strategies, infrastructures, training and other similar measures that have been established in some European countries but not in Portugal.

Clinical research is one of the activities with the highest return on the investment in the country. Thus, in the middle of austerity, this activity should be a priority of the country (28).

1.2.2. Pharmacovigilance

1.2.2.1. Pharmacovigilance and its historic evolution

No drug which is pharmacologically effective is entirely without hazard. Furthermore, not all risks are known before a drug is approved for commercialization.

Serious drug scandals that occurred from 1848 until the mid 1900s showed the need for laws to protect patients from unsafe medicines, and promoted the creation of governmental agencies and regulations to oversee drug manufacture, distribution, and prescribing practices (32).

1906 saw the implementation of the "Pure Food and Drugs Act" which prohibited interstate commerce of adulterated food and drugs and regulated labelling. In other words, this act prohibited false announcements and obligated the disclosure of all substances included in a product. This act did not contain safety or efficacy requirements; however, it gave some authority to the FDA to withdraw drugs from the marketplace without evidence of their purity (32).

In 1937, the sulphanilamide incident (an iatrogenic disaster caused deaths of more than 100 people by poisoning with ethylene glycol, used as solvent in the preparation of the medicine elixir sulphanilamide for streptococcal infections) prompted an urgent need for change. Therefore, it was implemented in 1938, the "Federal Food, Drug and Cosmetic Act" which requires tests to demonstrate the low toxicity of medicines before commercialization.

Another important scandal was the thalidomide disaster. Thalidomide had been introduced as a safe and effective hypnotic and anti-emetic drug. It rapidly became popular for the treatment of nausea and vomiting in early pregnancy. Tragically, the drug proved to be a potent human teratogen that caused major birth defects between 1961 and 1962. The thalidomide disaster led to an amendment of the previous Act which required that a product must be proven not only safe but also effective. All of these adversities led, in Europe and elsewhere, to the establishment of the drug regulatory mechanisms of today. These mechanisms require that new drug shall be licensed by well-established regulatory authorities before being introduced into clinical use (32).

Currently, all medicinal products in the EU are submitted to a strict assessment of their quality, efficacy and safety before being placed on the market. Once authorised, the monitoring process of medicinal products continues, to ensure that any aspect which could impact the safety profile of a medicine is detected and assessed, and consequently, that any necessary measures are taken. This monitoring process is called pharmacovigilance and can be defined as the study of the safety of marketed drugs under the practical conditions of clinical use in large communities (32,33).

Pharmacovigilance involves several stakeholders, such as patients, health professionals, regulatory authorities including EMA and pharmaceutical companies. Pharmacovigilance activities include:

- Collection and management of data on the drugs' safety;
- Evaluating the data to detect possible safety issues;
- Minimization of any potential risks associated with the use of a drug;
- Audits;
- Communicating with and informing all stakeholders and the public (33).

With the aim of facilitating these activities some tools and databases were developed such as the Eudravigilance (developed by EMA) and Vigibase databases (developed by World Health Organization (WHO)) to collect data about adverse reactions and the ICH Medical Terminology for Drug Regulatory Authorities (MedDRA). MedDRA is a dictionary used internationally during regulatory activities.

1.2.2.2. Pharmacovigilance in clinical trials

The regulatory authorities monitor the safety of the utilization of one investigational medicine during a clinical trial in order to permanently assess the benefit-risk relation in which was based the authorization to conduct that clinical trial. If this safety is not assured, the regulatory authority can suspend or repeal the previous authorization (34,35).

This vigilance is assured through the management and assessment of SUSAR's notifications, the annual safety reports (also known as Development Safety Update Report (DSUR)) and other safety information to detect possible safety signals. To put this in practice, EMA launched in 2001 the *Eudravigilance portal* which is an information system to manage information and to report electronically SUSARs occurring during clinical trials (34).

All of these aspects are described in the "Communication from the Commission — Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use" ('CT-3'). This detailed guidance is based on the Clinical Trials Directive, already mentioned, and is part integrant of the chapter 2 of the volume 10 of the EudraLex (34).

1.2.2.3. The regulatory framework of pharmacovigilance in Europe and Portugal

The 197.000 deaths per year in the EU concerning ADRs were the basis for the development of new pharmacovigilance legislation, in 2005. The aim of this legislation is to reduce the number of ADRs by collecting better safety data on medicines, assessing safety related questions, performing effective regulatory actions, empowering patients and increasing the transparency level and communication (34,35).

In 2012, the pharmacovigilance legislation was amended to strengthen the protection of patient's health by allowing prompt notification and assessment of possible safety problems by patients.

Thus, the legal framework of pharmacovigilance for medicines marketed within EU is provided by the (34):

- Directive 2012/26/EU of the European Parliament and of the Council of 25th October 2012 which amends Directive 2001/83/EC as regards to pharmacovigilance (36).
- Directive 2011/62/EU of 8th June 2011 which amends the Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards to the prevention of the entry into the legal supply chain of falsified medicinal products (37).

These two directives were transposed to the Portuguese law by the Decree Law nº 128/2013 of 5th September which is the 8th alteration to the Decree-Law nº 176/2006 (38).

- Regulation (EU) Nº 1027/2012 of the European Parliament and of the Council of 25th October 2012 which amends the Regulation (EC) nº 726/2004 regarding pharmacovigilance (39).
- Commission Implementing Regulation (EU) Nº 520/2012 of 19th June about the performance of pharmacovigilance activities provided in Regulation (EC) Nº726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council (40).
- Commission Implementing Regulation (EU) Nº 198/2013 of 7th March 2013, which introduces a black symbol on the product information of medicinal products for the purpose of identifying the ones that are subject to additional monitoring (33).
- Commission Delegated Regulation (EU) Nº 357/2014 of 3rd February 2014 supplementing Directive 2001/83/EC of the European Parliament and of the Council and Regulation (EC) Nº 726/2004 of the European Parliament and of the Council as regards situations in which post-authorisation efficacy studies may be required (33).

In addition to legislation, there are practical measures to facilitate the performance of pharmacovigilance activities that are the guidelines on Good Pharmacovigilance Practices (GVP) (34,35). GVP guidelines apply to marketing-authorisation holders, EMA and regulatory authorities in European member states and cover medicines authorised centrally as well as at a national level. The GVP guideline is divided into two categories: modules covering major pharmacovigilance processes and product or population specific considerations (34).

Consequently, the EU pharmacovigilance system is now one of the most sophisticated and comprehensive systems in the world developed with the goal of ensuring a high level of public health protection throughout the Union.

1.2.2.4. The National Pharmacovigilance System

In Portugal, the NPS was created in 1992 (some years after the recommendations of WHO), initially in a centralized format. However, in the following years, the system was decentralized with the intention of increasing the proximity of the system to health professionals.

Currently, the NPS has four regional pharmacovigilance centres which guarantee the proper collection, processing and evaluation of spontaneous reports of ADRs to ensure the protection of public health. Other important functions of each pharmacovigilance unit are the promotion of the system among health professionals to increase spontaneous reporting of ADR, always in collaboration with INFARMED (41). These four units are: the Northern Regional Pharmacovigilance Unit, the Centre Regional Pharmacovigilance Unit, the Southern Regional Pharmacovigilance Unit and the UFLVT. The autonomous regions of Azores and Madeira report ADRs directly to INFARMED.

Over the years, the NPS has been working in accordance with the EU requirements. As already mentioned, in 2012, a new legislation of pharmacovigilance was created making several changes. The main changes were: the possibility for patients to report possible ADRs; a more comprehensive concept of adverse reaction; all ADRs must be reported, regardless of seriousness and expectedness; the creation of the *Portal RAM* (an online portal for the electronic submission of ADRs used by notifiers and regulatory authorities); the requirement for a risk management plan to obtain marketing authorization; and the requirement for post-commercialisation studies or additional monitoring to any authorised medicine (37,38).

1.2.3. Data Management and Medical Writing

Data management can be defined as the process of controlling the information generated during a research project in compliance with regulatory standards. Any research will require some level of data management, including clinical research.

The management of clinical data has the purpose to generate high quality and reliable data to get as much information as possible from the study and to keep the number of errors and missing data as low as possible. This helps to create a drastic reduction in time from drug development to marketing. Some procedures of clinical data management include the design of case report forms (CRF), CRF annotation, database design, data entry, data validation, discrepancy management, medical coding, data extraction and database locking (42).

Medical writing encompasses different kinds of work, such as the preparation of regulatory documents to submit to regulatory authorities (e.g. common technical document, patient information leaflets, and DSURs) and research documents (e.g. clinical trial protocols, informed consent, and investigator's brochure). Furthermore, medical writers help write research articles, monographs, sales training materials, press releases. Medical writers also write about research discoveries for medical journals, web sites and newsletters (43).

2. On-the-Job Training

2.1. General Training

This section includes the description of some extra activities that I participated during this internship. These activities include a GCP Course which is an essential requirement for people who work in clinical research, an Intensive Course in Pharmacovigilance and also other activities as the Journal Club and Wednesday Afternoon Meetings which are important to know the projects of CPU members or collaborators.

I think these activities were very useful to learn some concepts and to improve my critical thinking. Another activity was the training session about IMM that I will also describe, briefly.

2.1.1. Training session about the *Instituto de Medicina Molecular*

In the beginning of my internship I had to attend a training session related to the IMM. In this presentation, I was given an overview of, the institution's objectives, policies, departments and ongoing projects. This training session also included a visit to the facilities of the IMM, including laboratories, scientific equipment rooms and other support departments that could be important for the new trainees during the internship.

2.1.2. Good Clinical Practices Course

Every year, the CPU organise a GCP course to all professionals involved on clinical research. In 2015, the course was on December 4th and I had the opportunity to participate and obtain my first GCP certificate. This course had the participation of some professionals of the IMM and INFARMED as speakers who talked about regulation, responsibilities of each stakeholder, essential documents, safety reporting and practical aspects of conducting a clinical trial.

2.1.3. Intensive Course in Pharmacovigilance

From November 16th to November 19th, I had the opportunity to participate in an intensive course in pharmacovigilance promoted by the Safety and Drug Utilisation Research Subunit. I had already done this course before my curricular internship in IMM, however, in 2015 I had the opportunity to participate in the course again.

The course was lectured by Dr. Mário Miguel Rosa (medical coordinator in the UFLVT and clinical pharmacology expert in EMA), Dr. Ana Marta Anes and many other health professionals. The main topics focused during the course were: ADR's mechanisms, risk-benefit assessment, pharmacoepidemiologic studies, methods for medicines' safety monitoring, ADR's spontaneous notification, imputation and causality assessment system and others.

2.1.4. Journal Club

Every Wednesday, the investigation team members of CPU gather at 8a.m to attend the Journal Club in the Clinical Trials Subunit. Each week, one member is assigned to describe a recent published article in the field of neurology and neurosciences. Normally, a short discussion starts about the design of the study, the potential therapeutic applications of the article findings, amongst other relevant topics. These discussions I attended were particularly interesting due to the different backgrounds of the team members and the sharing of information. In these meetings, I learnt some interesting concepts, especially about PD but also other neurologic diseases. Furthermore, discussions regarding study design allowed me to improve my critical thinking and identify the issues or weaknesses of a study when I read some scientific articles.

2.1.5. Wednesday Afternoon Meetings

Twice a month, on Wednesday afternoon, at 6 p.m., a CPU member or a person who collaborates with the unit presents an ongoing or future project, in the LCPT.

These meetings helped team members to get to know what everyone is working on, discuss the project, and provide feedback and opinions. One of the most interesting parts in these meetings were the discussions about the methodology of the project and all other aspects related with the planning and conduction of a project study.

I learned that the planning stages and conduction of a research project can be very challenging because there are always issues to solve and methodological limitations that cannot be solved. I think these meetings are also advantageous for the person who presents the project because she/he can improve her/his project with the ideas shared in the meeting, which can be particularly enriching owing to the multidisciplinary team present in the meetings.

2.2. Specific Training

As previously mentioned, the curricular internship was performed in the CPU of the IMM on different subunits. Thus, during my internship I had the opportunity to work in a multidisciplinary environment and communicate with several professionals. My internship started in the Clinical Trials Subunit, which lasted of four months. Later on, I moved to the Biostatistics and Methodological Subunit where I stayed until 11st March 2016 and then I started my work at the Outcome Research Subunit. I ended my internship at the UFLVT carrying pharmacovigilance activities until the end of my internship. Figure 4 gives a time perspective of the activities performed by each subunit.

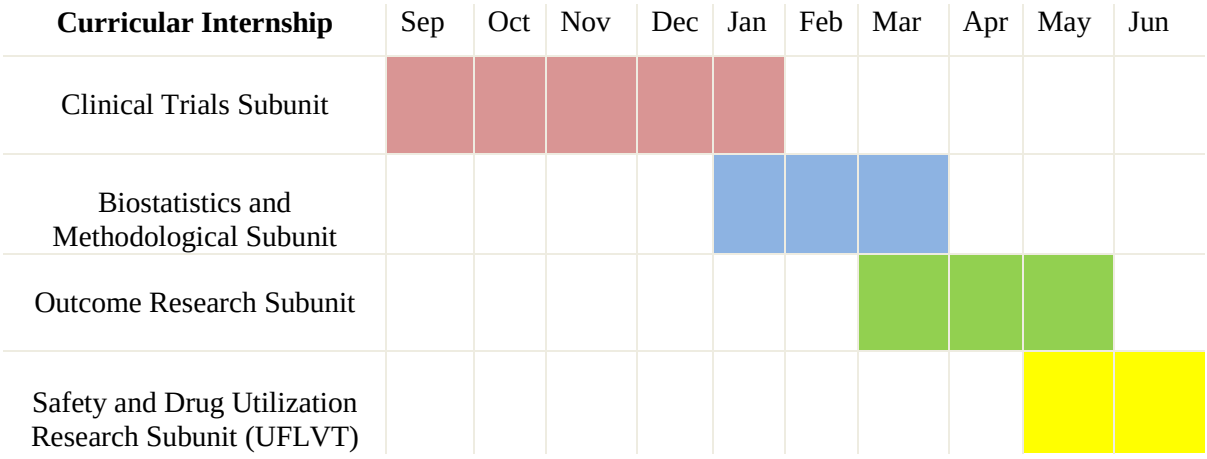

Figure 4- Schedule and duration of the internship activities.

The following sections illustrate the activities that were developed, divided by the units where I have worked in.

2.2.1. Clinical Trials Subunit

2.2.1.1. Introduction to the tasks of a Clinical Trial Coordinator

From September 2015 to January 2016 I worked as a clinical trial coordinator trainee in the Clinical Trials Subunit under the close guidance of Dr. Ana Noronha and Dr. Ana Salgueiro.

In the first week of the internship I received an overview of the clinical trial site, the procedures in place, where the material was stored, how to use the CRFs of the different studies and the general workflow of the centre amongst many others things. Furthermore, during this week, I read a number of study protocols and other relevant documents of the investigator's file of active

clinical trials. This part was important for my integration because it allowed me to have a better grasp of the documents involved in a clinical trial and where I could find vital information to conduct a clinical trial. Some of these documents included the study protocol, which is the guiding document of the clinical trial, the investigator's brochure, which provides detailed information on the investigational product, and the site delegation log in order to know the members involved in the clinical trial and their functions.

After this initial training, I started my coordination activities with PROTEC study (described in section 2.2.1.3) by entering the information of already realized study visits on the electronic CRF (eCRF), organizing the patients' dossiers and sending questionnaires filled by the patients to the sponsor of the study. Since I was in a completely new environment, I spent much time of the first week asking questions related to the procedures and receiving important feedback on my work.

Throughout the internship, I worked in areas that are universal to almost all clinical trials such as: archiving source documents and filling eCRF, processing and sending laboratory samples, measurement of vital signs and preparing medical visits and other medical procedures.

Following the initial training, I began working in earnest with my colleagues in all active studies of the subunit. This initial task division however, where everyone worked in the same studies, was not ideal. Consequently, the studies were divided by each trainee and I assumed the responsibility of coordinating three MS clinical trials, with the support of Dr. Ana Noronha.

In this phase, I studied more from these protocols to know all the aspects of my clinical trials, the site delegation logs to identify the team members of each study, and I organized some materials in order to simplify the management of the trial. I also studied the laboratory manual in order to process and to send biologic specimens as required by the central laboratory. I carefully read the patients' dossiers to identify the following study visits and procedures for each patient, to ensure that all procedures were made within the expected window avoiding protocol deviations. Then, I scheduled the following visits and procedures of each patient.

There were also other important tasks concerning inventory management that deserve management. It was very important that each study had enough study materials thorough visits. I had to verify each study, the laboratory kits needed for the next study visits, materials for unscheduled visits as well as the shipping documents to send the collected biologic specimens.

As a rule, in the day before of the visits I prepared all the materials needed for the visit to ensure that in the day of the visit everything was arranged to receive the patient. Usually, the subunit has more than one patient per day which obligated a strict management and organization, since there were many procedures with different team members occurring simultaneously. Thus, sometimes it was not easy to coordinate clinical trials due to all logistic aspects and different availabilities of the team members.

After the visit, I entered the data in the eCRF and I answered to the open queries in order to maintain the eCRF without queries.

2.2.1.2. Implementing / Setting up and running a clinical trial

The implementation of a clinical trial is composed by several phases and involves numerous procedures:

- **The Feasibility Study**

When one sponsor has a new trial there is an evaluation to identify the countries with more potential to conduct the study. The purposes of this evaluation are to determine if the country has the patient population required by the clinical trial and to verify the interests of the potential principal investigators. Thus, a number of potential centers are selected to check if they are feasible to conduct the trial and then a feasibility questionnaire is delivered. This questionnaire aims to evaluate the clinical research site conditions, the principal investigator availability and, the main characteristics, challenges and requirements of the clinical trial for the research group. If the principal investigator has interest in conducting the clinical trial, he or she must provide some specific information about the site experience in clinical research, the target disease, resources and facilities available.

Subsequently, the sponsor evaluates the questionnaire results and all the information provided and gives a feedback. If the feedback is positive, the next step is an evaluation visit (44).

- **The Evaluation Visit**

This visit involves a meeting among the monitor (as the representative of the sponsor), the principal investigator and study coordinators. In this meeting, the confidentiality agreement is signed and then the study protocol is presented for the first time.

Thereafter, aspects like the availability of the team to conduct the trial, the existence of patient population required and discussion of the number of patients that should be recruited in the center, the necessary materials, conditions and resources and the previous experience of the center are evaluated. In case the site needs some material the sponsor will be requested to provide for it. Furthermore, if the sponsor had a past experience with the site, the visit is quicker because the site can just confirm the conditions by answering some questions.

If the center is selected, the next step is the clinical trial submission to all regulatory authorities (44).

- **The Study Submission**

This phase deals with the collection and preparation of the required documents for submission to regulatory authorities. These documents include the curriculum of the team members, the

financial contracts, some declarations of the site and other relevant documents. It is also in this phase that the submission deadlines and recruitment plans are estimated.

When all documents are prepared these are submitted to INFARMED, CEIC, CNPD and to the site administration to obtain all the needed authorizations for the study initiation (44).

- **The Initiation Visit**

The initiation visit consists in the preparation of the site to conduct the approved clinical trial. In this visit, the monitor gives formation to the team about the study procedures, provides all essential documents, and verifies all the needed materials and the support systems (e.g. Interactive Voice/Web Response System (IVRS/IWRS) to obtain the medication's lot number attributed to each patient. It is accomplished with all the site team members and represents the official launch of the study.

Following this visit the center should initiate the recruitment process as explained by the protocol (44).

- **The Recruitment Process and Follow-up**

When a patient is proposed to enter in a clinical trial by the principal investigator, the patient receives an explanation about the trial and is provided with the informed consent form. This document provides an overview of the clinical trial, and states the conditions, rules, rights and obligations of the patient when joining the trial. It is recommended for the patient to take the informed consent form home, for reflex ion and to discuss it with family members. If the patient agrees to participate in the study, he or she signs the informed consent form (44).

After this, follows the screening visit, in which the patient is evaluated to see if she or he fits all the inclusion and exclusion criteria. If, by the end of the screening, the patient fits all established criteria, the patient moves to the baseline of the trial where he/she could be randomized to one of the possible arms. After the patient is randomized to one treatment, the patient enters in the treatment period. During this period, the patient has to come to the centre in a regular basis to attend medical appointments and for collection of the required data. The nature of the data that is collected depends on the trial but in general this data includes the patient's compliance with study procedures, health status, possible adverse effects and drug accountability.

It is common, following the end of the trial, for open-label extension phases, where the experimental drug is given to study participants until the medicine is launched for sale, to be proposed to the patient.

Furthermore, there is also a follow-up phase where the patients are examined to detect adverse effects not detected during the randomized phase and to ensure participants' safety (44).

Throughout this entire process, the trial coordinator is a constant presence to support the clinical study by ensuring that everything is properly coordinated and documented. Furthermore, the clinical trial is constantly monitored by a sponsor's representative to make sure that the clinical trial is conducted in accordance with the protocol and GCP to safeguard the safety, rights and well-being of all participants (44).

- **The Study Conclusion Visit**

The end visit aims to verify and archive all study documentation, realize pending payments and notify the regulatory authorities. The sponsor has also to send the final study report to the regulatory authorities as required by law (44).

2.2.1.3. Information about the clinical studies

As already mentioned, during the experience as clinical trial coordinator I assumed the responsibility of coordinating three MS clinical trials while also providing support for other studies. These MS clinical trials were:

- **The ORATORIO trial**

The ORATORIO trial is a phase III, multicentre, randomized, parallel-group, double-blind, and placebo controlled study to evaluate the efficacy and safety of Ocrelizumab in adults with Primary Progressive Multiple Sclerosis and is sponsored by F. Hoffmann-La Roche.

The study's primary objective is to investigate the efficacy of Ocrelizumab compared with placebo in patients with Primary Progressive Multiple Sclerosis, as measured by the time to onset of confirmed disability progression over the treatment period, defined as an increase in Expanded Disability Status Scale (EDSS) (which is a common method of qualifying disability in MS and monitoring changes in the level of MS disability over time) that is sustained for at least 12 weeks, based on regularly scheduled visits. Other secondary objectives are: the change in 25-foot timed walk from baseline to week 120 and the percentage change in total brain volume as detected by brain MRI from week 24 to week 120 amongst others.

Upon completion of the blinded treatment, patients who could benefit from further treatment may receive open-label Ocrelizumab until the marketing authorization or discontinuation of the program.

When a patient exits from the trial it is recommended a last phase of follow-up to monitor B-cell until B-cell count has returned to the baseline value (45).

- **The EXPAND trial**

The EXPAND trial is a Phase III, multicenter, randomized, double-blinded, parallel-group, placebo-controlled study to evaluate the efficacy and safety of Siponimod (BAF312) in patients with Secondary Progressive Multiple Sclerosis followed by extended treatment with open-label BAF312.

The trial is sponsored by Novartis and its main objective is to demonstrate the efficacy of Siponimod (BAF312) relatively to placebo in delaying the time to 3-month confirmed disability progression in patients with Secondary Progressive Multiple Sclerosis as measured by EDSS. The secondary objectives are to demonstrate the efficacy of Siponimod relatively to placebo in delaying the time to 3-month confirmed worsening of at least 20% from baseline in the timed 25-foot walk test and to demonstrate the efficacy of Siponimod relatively to placebo in reducing the increase in T2 lesion volume from baseline to the end of the study (46).

- **The PROTEC study**

PROTEC is a multicenter, open-label study to evaluate the effectiveness of oral Tecfidera (Dimethyl Fumarate) on MS disease and patient-reported outcomes in subjects with Relapsing-Remitting Multiple Sclerosis in the real-world setting.

The primary objective of the study is to estimate the annualized relapse rate in subjects with Relapsing-Remitting Multiple Sclerosis who are treated with Dimethyl Fumarate over a 12-month period (47).

ORATORIO and EXPAND trials were very complex trials to coordinate especially due the design of the studies and the large number of procedures to carry out in each visit.

The clinical trial where I had more activity was the ORATORIO trial because this trial was in the transition phase to the open-label phase of the study during my internship. As a result, some alterations in the procedures of each visit were implemented. I had the opportunity to participate in the Site Initiation Visit (SIV) of this new phase where the monitor of the study gave some information about the open-label phase. To ensure the correct application of the new procedures I had to create checklists for the ORATORIO trial with the activities for each visit. Furthermore, I created these checklists to simplify the work of the principal investigator and to ensure that all medical information was collected as required by the protocol and was registered in the patient's dossier. There was a great concern to ensure the accuracy and quality of the data collected. This concern during the development of the trial facilitated my work when I had to prepare monitoring visits because at the moment of the monitoring all the documents were organized and the medical data registered.

2.2.1.4. Description of the activities involved in clinical trial coordination

Now, I will describe the activities that I developed during my experience as clinical trial coordinator, following a work week format. The work starts with the identification of the medical appointments for the next days and the preparation of these visits.

- ***Preparation of patient appointments***

After verifying the patient's calendar, I scheduled with the team members needed for the respective visit a day within the expected window to receive the patient. Then, I asked the patient, by phone, if he could attend the study visit, in the proposed day.

During the telephone contact, I scheduled the visit with the patient and gave some relevant information (e.g. to bring the study's medication, to come fasted, if applicable).

In some trials I had to schedule transportation to the patient between hospital and the patient's home.

In the day before each patient's appointment, I had to study the procedures defined in the protocol flowchart and prepare all the required material for the visit. Normally, these materials were the patient's dossier with the medical files, the IVRS/IWRS sheets, the pharmacy prescription forms, the study checklists, the vital sign form, the electronic tablet to apply some neurologic scales (e.g. EDSS) and the laboratory kits. All these materials were also identified with the study ID of the patient to avoid material changes between patients of other studies, mainly when the centre had multiple patients in a single day.

- ***During the patient appointment***

When the patient arrived to the centre, I measured and recorded vital signs under the supervision of Dr. Ana Noronha who also performed the electrocardiogram (ECG).

I would then accompany the patient to collect biological samples by the assigned study nurse. After the blood and urine samples were collected I took the patient as well as the vital signs form and the ECG to be evaluated by the principal investigator.

While the investigator evaluated the patient I processed the biologic samples according to the laboratory manual. I will explain the processing of biological specimens in a more detailed manner later.

While the samples were in the centrifuge, I completed the IVRS or IWRS, depending on the study, and I filled the pharmacy prescription form with the lot medication number, the investigator signed, and then I sent to the pharmacy trough email. Some time after the request the pharmacy sent the medication to the centre to be delivered/administered to the patient by the investigator or

by the study's nurse. In some studies I received the returned medication (medication used by the patient) and returned it to the hospital pharmacy.

Once the investigator finished the examination, I confirmed if all the checklist topics are filled to ensure that the investigator made all the required procedures.

During my training, some protocols were amended and then the patients had to sign new informed consents. This task was performed by the principal investigator.

For patient expenses, Dr. Ana Noronha asked the patients to bring receipts of the expenses in order to reimburse the patient.

- **Measurement of vital signs**

I received training in measuring vital signs such as blood pressure, pulse, temperature and respiratory rate by one of the study's nurse. Consequently, I made these procedures in schedule visits as required by the protocol. This allowed the principal investigator to save time, as the values were already collected, and all it was needed was to evaluate them.

- **Processing of laboratory samples**

Each clinical trial had a laboratory manual providing all the instructions to collect, handle, process and ship the required biological specimens, which were mainly blood and urine.

All laboratory kits needed for a given visit were identified with the visit number and patient's study ID number. Therefore, after I selected the correct kit I checked, every previous Friday, if some required sample had to be sent in dry ice, to request dry ice in advance before the study visit.

After the biological samples were collected I read the instructions to process these samples. Some of the blood samples needed some time to clot and others had to be centrifuged immediately. Then, I programmed the centrifuge as explained in the laboratory instructions and started with the processing process. After centrifugation was over, I transferred the plasma to the transfer tubes. In some trials I also made blood smear preparations to be evaluated by the central laboratory.

Once all samples were processed, I prepared them for shipping in the proper boxes and with the required shipping documents. Usually, each central laboratory had its own boxes. For the samples that had to be shipped in dry ice, I waited for courier services to bring the dry ice and during this time I put the samples in the fridge. When the shipment was ready, I called the courier services to pick up the ambient and refrigerated samples.

➢ ***After the patient appointment***

- **Entering data in the eCRFs**

As soon as the visit ended and all the biological material were ready for shipping, I entered the data on the eCRFs of the different studies as required by the sponsor.

All data from each patient participating in a clinical trial is required to be documented in the eCRF. Then, when I had to introduce the patient appointments on the eCRF I checked in the patient's dossier if the investigator had documented some new information about adverse effects, concomitant medications or any other additional procedure to ensure that all the data on the patient's file was also documented in the eCRF.

Whenever there was an incoherence with the data that was introduced, the clinical study data manager will open a query in the eCRF asking for additional clarification or pointing out an error. In these cases, we had to see what the source of the query was and answer it in a prompt manner. This required a multidisciplinary effort since many queries required the input from physicians, raters, nurses and study coordinators.

- **Archiving the documents**

Each study had its own cabinet where the documentation was stored and safely archived. Normally, a study's visit involves a significant amount of documentation such as the checklists with the medical examinations, the laboratory results, the vital signs form, the IVRS/IWRS sheet, the ECG result, and many others. All of these documents must be properly archived in the respective patient's dossier after they are signed and dated by the principal investigator. Documents such as study financial contracts, amendments to the protocol and other study materials which sometimes are modified by the sponsor needed to be archived in the correct investigator's files.

In fact, organization is crucial in clinical trials because if one document is archived in the wrong place it leads to confusion and the enormous risk of losing vital documentation. This is very frowned upon by the clinical trial sponsor (represented by the monitor who evaluates all of these dossiers) because it shows that the clinical research centre has organizational issues.

➢ ***The Friday Tasks***

Every Friday was characterized by specific tasks in order to prepare the following work week. Thus, on Fridays I saw the agenda to verify if there was some patient for the next week. If I had some patient I studied the protocol in order to know what procedures should be done in the visit and what I had to do. Then, I checked who were the members needed for the visit and I sent the week calendar to inform them about their tasks in the following week. When the visit had

medication dispensation or medication administration I also informed the pharmacy to organize and expedite its own work. It was required that all study coordinators of the centre schedule their study visits in the unit's calendar, in order to inform all the team members of each study. This is very important to organize the centre, since it allows every member to know what everyone is doing in a given work week.

I also verified the laboratory kits corresponding to each visit to confirm if there were sample to send in dry ice and made the respective request to ensure its arrival in the day of the visit.

The Mondays' visits were always prepared on Fridays to ensure that in the day of the visit everything was arranged to receive the study's participants.

- ***Preparing the monitoring visits***

The monitoring visits consist in visits conducted by a monitor to the site to verify the compliance of the data collected. Monitoring visits are an essential piece of the clinical trial puzzle, as they ensure the safety, rights and well-being of participants as well as the quality of data and the compliance between procedures performed and the study's protocol.

When the centre had a monitoring visit, I organized all the data a few days in advance. I also resolved queries and reviewed if the pending issues from the last monitoring visits had been already answered. In the day of the monitoring visit, the monitor reviews the source documents and discusses with study's coordinators and investigators some questions to clarify and solve possible issues.

- ***Activities in free time***

When I did not have any patient scheduled for a day, I usually confirmed the patients' calendars to ensure that all of the following procedures were scheduled with team members and with the patient.

I also checked if the centre had the materials needed to the next visits. Then, I verified the laboratory kits to the upcoming three or four visits of each patient to ensure that in the visit days all the needed material was available. If the centre did not have the material I requested the material by fax or online, depending on the clinical trial. Furthermore, I also checked the expiration date of the laboratory kits to ensure that the already expired kits or near expired kits were destroyed by the qualified lab technician of the centre. This is a very important task to avoid the use of expired kits which constitutes a deviation and leads to the annulment of the biological specimens' analysis.

Another task developed in my free time was the inspection of the eCRFs of each study, to answer queries and verify if the data was complete and up to date. Thus, I opened all eCRFs and I

answered to the opened queries. Sometimes, I had to ask the support of Dr. Ana Noronha, the study's monitor or the principal investigator to answer some queries.

In addition, I also used this free time to solve some pending issues with the principal investigator.

When I had everything organized I read other studies' documents or I helped my colleagues in other tasks.

2.2.1.5. Other activities

- ***REGISTRY monitoring visit***

During my internship in the Clinical Trials Subunit I was also involved, to a minor degree, in the REGISTRY study which is a multicentre, multinational, prospective observational cohort study of the European Huntington's Disease Network with the purpose to follow a large number of HD's patients and controls to further characterize the disease and to develop and validate sensitive and reliable outcome measures for detecting onset and change over the natural course of the disease (48) .

The HSM-CHLN is the Portuguese language coordinator centre which means that it is responsible to coordinate and monitor all the Portuguese centres which participate in this study.

Therefore, I had the opportunity to participate in one of these monitoring visits to the *Hospital Doutor Fernando Fonseca, EPE*, with the current national coordinator Dr. Ana Salgueiro. This monitoring visit was a very interesting and challenging task because we had many patients' dossiers to see and to make source data verification to ensure the quality of the data. Furthermore, we evaluated the investigator's answers to the eCRF's queries and we confirmed if these answers were registered in the clinical process of the patients. When everything was well-registered and the quality of data was assured, we removed the queries. In cases where we did not find some relevant information we launched new queries to the investigator or we reopened queries already launched if we couldn't confirm the respective answers.

This activity showed me the complexity of a monitoring visit mostly due to the different organizational nature of each site. Accordingly, I learnt that when we have to do monitoring visits it is imperative know what we have to do in each visit to ensure that the visit is conducted in a proper way.

- ***ORATORIO Site Initiation Visit***

The ORATORIO trial had a transition to the open-label phase during my internship in the Clinical Trials Subunit.

This new phase involved some protocol and procedure alterations and because of that the centre had one SIV in which I had the opportunity to participate with Dr. Ana Noronha and Dr. Ana Salgueiro. In this SIV we were given an overview of the aspects of the clinical trials that changed in this new phase of the study, which included, the informed consent, some visit procedures, the new support documentation and the new laboratory kits. I participated actively in this SIV, asking about some important aspects that needed additional clarification, such as how the new informed consents were to be signed, and how use the new laboratory kits which had some specificities in comparison with the older ones.

2.2.2. Biostatistics and Methodological Subunit

The work in this subunit was constituted by diverse projects and I will talk about them in the following subsections:

2.2.2.1. The Huntington's disease statistical models project

During my first week in Biostatistics and Methodological Subunit I started with a project in HD that sought to describe what statistical models have been used in scientific papers illustrating the characteristics of HD and disease's progression.

I was instructed to collect some important parameters of each scientific paper previously selected through a search strategy. At the end of this work, Dr. Nilza Gonçalves crossed the information collected by me with the same topics already collected by the subunit team members to validate this work before taking conclusions. Furthermore, I selected more scientific papers about this topic in accordance with some criteria to complete the search and then I made the same work of information collection.

This work was internationally presented by the biostatisticians of the subunit.

2.2.2.2. Not to do recommendations in Parkinson's disease project

Considering my interest in making a systematic review, Professor Joaquim Ferreira proposed me to make a review of the negative recommendations of the existing clinical practice guidelines for PD and then write and publish a scientific article.

This work has been made by the English authority – National Institute for Health and Care Excellence (NICE) which writes several clinical practice guidelines and highlights the "Do not do recommendations" mentioned in that guidelines to improve clinical practice.

My systematic review aims to review the most important guidelines in PD and to collect the negative recommendations with their evidence level. After all relevant data was collected the collected negative recommendations were represented in a table in which it is possible to verify

how different guidelines can have different/contradictory recommendations or the same recommendation but with different evidence levels. Another interesting part of this work is the possibility of verifying the chronological evolution of some recommendations, from 2000 to 2016.

The initial phase of this project was the research of the current guidelines for the management of PD. The search strategy was based in a previous work made within the subunit by a medical student which evaluated published guidelines on PD with the AGREE instrument. Therefore, current and updated clinical practice guidelines on PD were searched in different databases such as *PUBMED, the American Academy of Neurology database, the Guidelines International Network database, the International Parkinson and Movement Disorder Society database, the European Academy of Neurology database* and *National Guideline Clearinghouse database*. The search results were screened and just the guidelines which include the term "Parkinson's disease" in the title and which were written in English language were included. This screening and management of clinical practice guidelines was made with ENDNOTE software.

The second part of this work was to collect the negative recommendations of each included guideline. In this initial phase, with the aim of collecting as much information as possible and to avoid missing information or other mistakes I tried to be very comprehensive. Then, I considered as negative recommendations all the recommendations which were obviously negative recommendations (i.e. recommendations with negative words such as "should not", "not recommended" and many others) and cases where no recommendations were made because there was no evidence to recommend anything. The recommendations written in a positive way but with a negative "tone" were also included in this phase. With this I created an Excel document with information about the guideline, the recommendation and the corresponding evidence level. In discussion with Professor Joaquim Ferreira, we decided that only the "pure" negative recommendations would be included in this work.

After that, a new table was made to classify all the selected recommendations in predefined groups (i.e. diagnostic or treatment) and subgroups which were related with the different kinds of diagnostic (such as imaging, drug challenge tests, olfactory tests and other diagnostic tools) and related with treatment of PD (such as prevention of motor complications, treatment of parkinsonism, treatment of motor fluctuations, treatment of gait disorders, treatment of depression, treatment of dementia, treatment of psychosis, neuroprotection amongst others).

Afterwards, similar recommendations of different guidelines will be clustered in one recommendation. With this exercise, we hope to have a comprehensive Excel database of "Do not do recommendations", see how different guidelines recommend one way of treatment and/or diagnostic for the same condition of PD and also how different guidelines classify the same

recommendation in respect of evidence levels. However, taking into account the complexity of this work, this project it is not finished yet.

2.2.2.3. Other activities

Still in the Biostatistics and Methodological Subunit of Joaquim Ferreira Lab I was involved in other minor activities that I will mention with less detail.

Every year, each IMM's laboratory has to make an activity report and submit to IMM which compiles the information of all laboratories to make the institution report of the year. I was proposed to participate in the elaboration of the CPU's report corresponding to the activity of 2015. I was tasked with collecting bibliometric information for all articles published in 2015 by the Joaquim Ferreira Lab's affiliated authors. Furthermore, I also had to collect other bibliometric information such as the number of references, the number of citations, the h-index and the accumulated impact factor of each author. This information was collected using online websites and tools such as *Web of Science*, *ResearchGate*, *Google Scholar* and others.

Another important activity of Joaquim Ferreira Lab is the article submission for scientific journals. This is a task which involves a significant amount of work and time because each scientific journal has its own specificities and rules which have to be studied before submitting the article to avoid the refusal of the article. Then, the article has to be edited in some fields as requested by the journal rules. I have the opportunity of participating in this submission process of some lab's investigators articles, learning in a general way how to submit an article to a scientific magazine and about the phases since submission up to the acceptance of the article for publication.

As a general rule, in multicentre studies, all documents are written in English language. However, some of these study's documents have to be translated into Portuguese when the study is done in Portuguese sites to obtain an authorization by the competent authorities for the study accomplishment. For that reason, I also had to translate an English document important for the study in Portuguese in order to submit it to the Portuguese authorities. This was one of the activities of medical writing that I had opportunity to do.

2.2.3. Outcomes Research Subunit

2.2.3.1. The ALFABETO study

The ALFABETO is an observational, prognosis study whose aim is to identify prognostic factors of high-flow oxygen therapy in pediatric patients with acute bronchiolitis. In other words, the study seeks to identify children who will benefit from this treatment and the children who probably will need a more intensive treatment.

This is a multicentre study done in HSM-CHLN and other hospitals of Lisbon. This is a simple study in regards to the materials needed, as each centre has all the material needed to include patients, and it is only a question of recruiting patients who meet the eligibility criteria. Furthermore, some weeks after the patient inclusion in the ALFABETO's study the investigators have to make a telephonic contact to the parents of the child with the intention of evaluating the health evolution of the child after the use of the technique in study.

My work with this study was to introduce the collected information in the eCRF and at the same time monitor this information in order to detect possible inconsistencies in the information collected by the investigators of the different centers. Although this is an observational study, the monitoring task was essential to ensure the quality of the data collected and consequently increase the power of the study.

Furthermore, I was responsible for contacting the investigators of other sites to manage the shipping of the filled CRFs and to give some support to these investigators in some possible doubts or questions, mostly about GCP, that needed to be applied in the study and which were not completely known by the investigators.

2.2.3.2. Investigation about the hypothesis of bias introduction on the final results of one study due to interim analysis

During my training in the Outcomes Research Subunit I had the opportunity to work in a project which sought to better understand the influence of interim analysis and its disclosure on the final results of the study. This is a very pertinent doubt because it is common practice for clinical studies to have interim analysis during their progression, with the results being frequently published, especially for bigger trials. Consequently, the investigators who have access to the results of interim analysis can change their opinions and their way of evaluating the study subjects, introducing bias in the research study.

Professor Ricardo Fernandes proposed me to make a research using published study reports on *Cochrane Library* and *PUBMED* in order to answer this question. Therefore, a simple search using the term "interim analysis" and time filters was made. I used time filters on the search strategy with the aim of obtaining information about finished studies because just these have an interim analysis report and a final study report. Recently published interim analysis were not analyzed because they did not have a final report yet. With this search strategy I obtained a lot of articles reporting interim analysis results of one study and systematic reviews which include results of interim analysis. For articles which report the interim analysis results of one study I searched for the corresponding final report. After that, I analyzed at random approximately 100 of the search results, article by article. During this research, I looked for remarks or comments of articles' authors in written text of their

opinions on the possible introduction of bias on the final results of the study due to the publication of interim analysis results before the end of that study.

Only some of the evaluated *Cochrane* reviews discussed the question in the characterization of included studies. In fact, some of these reviews consider the publication of interim analysis results as "other bias" and classify it as high risk of bias or as unclear risk.

Despite this analysis it was not possible take a significant conclusion about the question because this topic is not mentioned in a big number of articles. In other words, the authors just publish the results of the interim analysis and sometimes when the study finishes it is published a final report which only indicates that was made an interim analysis. Nothing is mentioned about the possible introduction of bias in the final results due to the previous publication of these interim results. This subject of whether there is an introduction of bias on the final results of the study due to the publication of interim analysis results before the end of that study warrants further research.

2.2.3.3. Prémios Científicos Universidade de Lisboa / Caixa Geral de Depósitos

University of Lisbon and *Caixa Geral de Depósitos* established a cooperation agreement to reward scientific research and to stimulate the practice of publication in international recognized scientific journals. Therefore, investigators at the University of Lisbon can apply to this award and gain financial support for a scientific research project.

The application to this award involves the preparation of several documents and calculations and I was responsible for the preparation of one application to one of the investigators of the CPU. To prepare the application I started with the elaboration of a list with all the articles published by the investigator between 2011 and 2015 indexed at the *Web of Science* platform as requested by the published regulation. After that, I analyzed each article to verify if it met all the requirements to be included. Furthermore, information about the number of citations, the number of authors, the name of each author, the journal of publication, the year of publication was also collected to complete that list using *Web of Science*. These indicators were also used to calculate the Quality Criterion of the author which will be the most important method of evaluation the applications by the jury. Subsequently, considering the calculation formula mentioned in the regulation I had to create an Excel document to put the given formula and calculate the Quality Criterion score.

Another requirement of the scientific award regulation was the submission of a Citation Report for the included studies. This Citation Report can be obtained in *Web of Science* and gives the information mentioned above.

With this work I could learn about how to use the electronic platform *Web of Science* and the basics of bibliometric indicators of an author/investigator.

2.2.4. Safety and Drug Utilization Research Subunit

2.2.4.1. Daily activities of Pharmacovigilance

As already mentioned, UFLVT was the subunit where I finished my curricular internship with pharmacovigilance activities.

The first week in the pharmacovigilance unit was an introductory week on the area with some explanations of Dr. Ana Augusto (pharmacovigilance technician and responsible for the quality management in the subunit) and Dr. Ana Marta Anes (the pharmaceutical coordinator) and with an extensive reading of GVP, Quality Management System (QMS) documentation and the book *"Farmacovigilância em Portugal*". The book details the NPS and its evolution. I was also given documentation about the MedDRA dictionary in order to understand its organization taking into account that it is an important tool used daily in the subunit.

The QMS has work instructions, orientations and procedures for almost all the activities developed in the subunit. Consequently, with these instructions and subunit collaborators' support I could integrate myself easier and I was able to start collaborating in the routine work in the pharmacovigilance subunit.

My first activity was the management of spontaneous notifications received in the subunit either by e-mail, mail, fax, and telephone or through *Portal RAM*. The first step is to validate the received notification. As a result, I verified if the report included the four basic pieces of information for a spontaneous notification to be valid: information about an ADR, a notifier, the patient who suffered the reaction and the suspect active substance. Moreover, the notification should be sent from the operation area of the unit and the suspected drug should be a drug and not a medical device or other pharmaceutical product, such as supplements, because these situations are not managed by the subunit. Afterwards, the received notification has to be dated and signed by the person who receives and manages it and an identification code is assigned to it.

After, the notified case is introduced in *Portal RAM* (if it was not already received by this way) always with the help of the MedDRA dictionary. When I started my internship I received credentials in order to have access to the portal with my own account.

The associated documents have to be archived electronically and in paper as well as the actions made to manage the ADR. The registration of the case information and all activities performed are very important to maintain the data archived during the time requested by law and also to meet with the obligations imposed by the QMS.

In this initial phase the information is introduced in the electronic portal but it is not submitted to the national pharmacovigilance system database (SVIG) because the case is not finished yet.

After this initial task, I was asked to analyze the received cases with the support of the Summary of Product Characteristics (SPC) in order to verify if there was some possible relation between the notified adverse event and the medicines taken by the patient and in this way understand or discuss, when necessary, the causality that would be attributed later by Dr. Mário Miguel Rosa (the medical coordinator of the subunit). Thus, in this SPC analysis I studied the therapeutic indication, the dosage regimens, drug contra-indications or precautions and drug interactions (if the patient was taking more than one medicine). Next, I compared this SPC's information with the notified case to verify if the suspect medicine was being taken according with SPC, to understand if it has some reason to believe that the reaction has been caused by the drug taken, and in a positive case, what is the assigned causality that should be attributed by the medical coordinator after the contacts to ask for additional information. UFLVT also contacts the notifier until the ADR's solution to know the health evolution of the patient.

Normally, the day after the notification reception is to obtain additional or missing information and, to confirm that the notifier is real the unit collaborators have to contact the notifier. During the internship I did not have the opportunity to do telephonic contacts with notifiers to obtain more information. This additional information which would be used to assess causality has to be collected and entered on SVIG within 7 calendar days after the receipt of notification.

Subsequent to the collection of additional information, a narrative of the ADR notification is written and the case is added in the SVIG with a copy of the original notification provided by the notifier. Following this, the pharmacovigilance department of INFARMED has access to the introduced data.

With all the information collected, the medical coordinator of the subunit assesses the case considering the SPC of the medicine, the temporal relationship, rechallenge (if a similar drug reaction has occurred in the past to the same individual), pharmacological plausibility and concomitant drugs to assign the more appropriate causality category which is included in the electronic *Portal RAM* and submitted in the SVIG, in 30 calendar days. The notifier is informed (with one causality letter) about the causality category attributed by the medical coordinator and the decision taken about what would be done or not with the medicine.

Finally, a causality report is written and the case is closed and archived as well as the original notification in the subunit archive.

As part of my functions, I wrote causality reports and letters before the causality assessment, with the field concerning the causality classification being filled by Dr. Mário Miguel Rosa. This was very important to expedite work taking into account the short timelines.

As the final step, an email is sent to INFARMED to inform that data entry is completed.

During this process, notifications are organized as: pending contact, causality already assessed and unprocessed notifications by the subunit (e.g. quality problems of the medicine without ADR, adverse events not related with a drug or ADRs of other regional units).

When my curricular internship finished I was able to perform these routine pharmacovigilance activities and understand the role that a pharmacovigilance unit plays in ensuring that public health is assured.

2.2.4.2. Audit

On the last week of my internship, the pharmacovigilance unit had an audit from INFARMED, who sent two auditors to evaluate the QMS of the unit and to verify if the previous corrective and preventive actions mentioned in the last audit has been done as recommended. Throughout the audit, the collaborators were available to the auditors to answer some questions. While I did not have an active role in this audit it was important to understand the need of keeping everything organized.

3. Discussion

Before I start talking about my experiences in each subunit I will present some opinions about the facts presented previously. As we saw in State of the Art subchapter, the number of clinical trials in Portugal is lower than in other countries in the EU as it is the case of Austria and Czech Republic, countries which shame a number of similarities with Portugal. However, these two countries have more clinical trials occurring by year, as already mentioned. Then, we can say that the number of clinical trials in Portugal has room to improve. Consequently, Portugal has a potential to increase the number of clinical trials and then approximate its capacity to other European countries.Taking into account the knowledge gained during this master's degree and considering the issues referred in the state of the art, I believe that the number of phase I trials will only increase with an increase in investment in specialized centres, and I feel this problem will not be solved by the new Portuguese law.

The new clinical research law solves some problems such as faster clinical trial approval times and clinical trials disclosure. However, other problems such as the investigator availability and lack of human and financial resources to invest in new structures will continue, and the number of clinical trials will remain low. It is paramount to review financial incentives and programs for clinical research, create dedicated management structures for clinical research, improve conditions for clinical trials in primary care and also rethink how clinical trials are positioned in a health professionals career and work. I think these two last measures could have a big impact in the quantity and quality of commercial and academic clinical studies made in Portugal, as during my experience in IMM I saw that some investigators have the wish to do clinical trials but do not have time to engage in them. Furthermore, during my internship some physicians were starting working in this field and I verified that they did not know some specific concepts of clinical research because their academic background is not directed to clinical trials practice. This showcases that there is an issue with training in clinical research.

In these situations the clinical trials coordinators (and monitors) play a very important role to ensure the appropriate conduction of clinical trials, to give support to investigators and to clarify doubts. Then, I believe that all clinical trials sites would gain a lot with professionally trained clinical trial coordinators.

During my curricular internship I was involved in several activities such as clinical trial coordination (which allowed me to closely observe the difficulties and problems mentioned above and reflect about them), data management, medical writing and pharmacovigilance activities. Thus, I contacted with a very complete and diversified team of qualified professionals.

As a clinical trial coordinator trainee I learnt a lot because there are some things that we can only understand when we are face to face with the real situations. In the beginning I had some difficulties in understanding all the tasks needed for each study. Furthermore, my colleagues and I were not very well organized because we did not divide the studies and consequently, all of us worked in all the studies at the same time. This way of organization was very difficult taking into account the complexity of the clinical trials and the big number of different procedures related with each study. To solve this issue, the studies were divided and I started coordinating the clinical trials in MS.

After this moment, everything was easier because I could specialize myself in that studies and just after that moment did I start to understand the order of tasks and procedures for my studies. In other words, only after this studies distribution did I feel comfortable to perform the coordination activities. Then, when I understood the activities and reached the capacity of playing an active role in the subunit I always tried to improve my performance. Consequently, I consider that I acquired skills in clinical trials coordination and I feel comfortable to perform the daily activities of a clinical trial coordinator, and this objective was completely reached.

Despite this distribution of studies, I was also involved to a minor degree in other clinical and observational studies. The Clinical Trials Subunit has a lot of on-going studies with a wide range of procedures to follow which involves a lot of different professionals such as neurologists, psychologists, monitors, nurses, laboratory technicians, pharmaceuticals and also several facilities. As a result, I could learn a lot with all of these professionals by lending a hand in a variety of studies. I could see the logistic problems and scheduling difficulties of each member. These difficulties were always solved by talking with the different team members and finding the solution that best fits everyone.

Throughout this internship, I learnt that it is necessary a very well organized team to perform all the procedures of a clinical research in compliance with all the imposed requirements. Normally, all of these points are managed by the clinical trial coordinator who has a very challenging and difficult role.

Organization was a great concern for me. Actually, I always verified if everything was well organized, signed and dated. In addition, I always scheduled the appointments in advance and prepared the visits in the best and easiest way to the investigators. All of these tasks were made by checking the protocol all the time to avoid protocol deviations. So, I always checked everything to ensure that nothing goes wrong in the clinical trial.

The Clinical Trials Subunit has a very good organization method; morning time is for the patients' visits and in the evening administrative and logistic activities such as data entry into the

eCRFs and preparation of future visits are performed. This kind of organization has resulted well because it avoids leaving accumulated work for the following day. Hence, I think this is a very good method that could be implemented in other clinical trials sites to improve their performance. In fact, I could observe the processes and the main problems involved in clinical trials, and see how these can be solved. These learning experiences will be very useful for my future professional life in the area.

Communication is a very important skill to work in this area and this was a skill that I had the opportunity to improve a lot. Throughout the internship I needed to work and communicate with a diversified research group including the study monitors. Thus, my initial objective of improving my personal and interpersonal skills was also reached.

In addition, it was possible to apply some concepts learnt during my academic life such as GCP guidelines which should always be present in the conduction of a clinical study. Other significant activities I had the chance to participate in the subunit were the REGISTRY monitoring visit to *Hospital Fernando Fonseca* and the ORATORIO SIV. These activities allowed me understand the role and duties of a monitor and I could observe how a monitoring and an initiation visit are conducted. In fact, I consider the monitoring area a very challenging area and these activities allowed me to see that it is a possible future work area in my professional life. To conclude about study coordination, I can safely conclude that the clinical trial coordinator is a fundamental piece to ensure that all the topics mentioned in the GCPs guideline are accomplished and the clinical trial is well conducted. I feel I am capable of working in this area autonomously. As a result, I think this experience in clinical trial coordination exceeded the objectives defined at the beginning of this internship.

During my training in the Biostatistics and Methodological Subunit I developed different kinds of activities which are not completely related with statistics. In fact, my training in statistics was scarce and I think this is the unique failure that I can point during the entire internship. In other words, I think my primary objective of acquiring basic knowledge about the application of statistical methods in research projects was not completely achieved. Normally, we had routine meetings with Professor Joaquim Ferreira in order to inform about the status of the activities of the CPU. In these meetings I had the opportunity to know some of the most interesting activities performed by the biostatistics subunit and grasp the basic functioning of a statistical unit. However, I hope to develop my knowledge in statistics because the contact with the projects of the subunit made me more curious about the area. Despite this, I could develop other interesting projects which involved a lot of data collection following strict methodologies. The most laborious work was “Not to do recommendations in PD project” which allowed me to learn a lot of since it was my very own research project. This project was not easy to conduct because I have never

conducted a project like this and consequently there are a lot of things that I did not know how to do. Then, I consider this project a big learning experience for future projects. This whole experience was a way for me to learn about proper search strategies and how to manage the search results with the ENDNOTE tool. I could practise data collection after I have studied the best method to collect it and then manage the collected data.

This task involved some problem solving, planning and critical thinking about the best approach of conducting the project and organizing the data in different tables in order to have the information organized in an easier way to work it. Furthermore, I also have to plan how I would organize the final data (after the data has been worked and the different recommendations have been aggregated in one recommendation) in a manner possible of publishing.

The most important notion I could grasp (with this project and with the general training described) is that the initial planning stages of a project are essential for its success. Furthermore, it is also essential to think on that is the best publication strategy since the beginning of a project, as taught by Dr. Márcio Barra and Professor Joaquim Ferreira. Following data collection I had my first contact with medical writing activities. I also get in touch with medical writing with the activity of an English document translation to submit to the Portuguese authorities. With these activities, mainly the research project in PD, I could improve my writing skills and my capacity to synthesise information as required in scientific articles. However, I think I have to explore more the area of medical writing to learn more about it because the activity developed motivated me more.

Subsequently, I consider that my primary objective of actively participating in a research project and develop methodologies to plan and conduct a project was fully reached.

In the Outcomes Research Subunit I could work in data collection of scientific articles and systematic reviews. Data collection is a vital task in the beginning of each work and it is critical having a very good understanding of the project's objectives to collect the needed information.

Another important task developed in this unit was with the ALFABETO's study. This is an observational study and I could verify the different requirements in comparison with clinical trials. With this study I performed activities of coordination (data entry in CRF) but the activity I would like to mention was the monitoring activity (where I made data verification). Accordingly, I verified the documents filled by the investigators to detect possible inconsistencies. Following these monitoring activities, I could build a simple idea about the role of monitors and their duties. This idea was also constructed with the REGISTRY monitoring visit to Hospital Fernando Fonseca as already described.

My internship finished in the pharmacovigilance unit and it was vital to obtain knowledge and practical skills in the processing of spontaneous notifications of ADRs, and to improve my knowledge about different topics of pharmacovigilance such as the National and European legal

framework, the NPS and the GVP guidelines. With this training I could experience how to introduce data in *Portal RAM*, how to code medical terms with the MedDRA dictionary and write causality reports and letters. Consequently, I participated in the entire process needed to manage a spontaneous notification until its finalisation. Furthermore, the work in this subunit is very well organized and everything is well documented allowing the information tracking. My experience in pharmacovigilance allowed me to acquire qualifications and skills to perform daily activities of pharmacovigilance as I had defined in my personal objectives. I consider that this was a great work experience and I it is a possible work area for my future job.

4. Conclusion

During this curricular internship I had the opportunity to contact with multiple areas related to clinical research because I could develop a wide range of activities with the support of people with different backgrounds. This allowed me to develop my personal, interpersonal and professional skills over the course of this internship. I feel I have improved my communication, organization, critical thinking, problem solving and autonomy skills. Moreover, it was an important way for me to know and understand my interests, capacities, strengths and weaknesses. For example, I enjoyed being responsible for the coordination of different clinical trials in different stages and with different requirements. Working as study coordinator allowed me to acquire several skills of coordination, especially when I was juggling three trials at the same time. Consequently, I now feel much more confident to perform this work in my future professional life with much more autonomy. In the Clinical Trials Subunit I could felt the agitation of the visits and the huge difficulty in coordinating all the procedures and team members involved in the clinical trial. The close contact with patients was also a good experience because I could talk with them and understand their problems and fears. I could also verify that some patients have a big need of attention and sometimes they have other troubles not only related with the disease. Actually, this was a very challenging work with which I learnt a lot professionally but also personally.

On the other hand, I have more difficulty in managing and developing a research project because of the impartiality and methodology that were completely necessary for the "Not to do recommendations in PD project". Despite the difficulties with this project I could learn and understand some weaknesses of my work and also how to improve it. Then, I consider this project useful because I learned for future projects and I think that in future projects I will manage the project with a different organization and methodology.

My work in pharmacovigilance unit was an excellent opportunity to understand the unit daily routines and to recognize the importance of having a quality system implemented which brings organization to the subunit and facilitates the collaborators' work.

In fact, my internship has become more than I ever expected due to the skills acquired and the achievement of predefined objectives and learning outcomes. However, sometimes the pressure to do the best possible is very nerve-racking and scary. But also this was important because I learnt how to manage this feeling to avoid a negative interference of it in my capacity of work.

To conclude, this work experience was really remarkable not only because the CPU is recognized by the excellence of its work but also due to the wide range of activities I could develop. Moreover, I also had the opportunity to put into practice the concepts learnt during the

degree and master’s degree and also to develop my professional skills which I think that will be vital for the start of my professional life.

5. References

1. Superior M da SM da C e T e E. Portaria 1371/2009, de 27 de Outubro [Internet]. Ministério da Saúde; Ministério da Ciência e Tecnologia e Ensino Superior; 2009. Available from: http://publicos.pt/documento/id483132/portaria-1371/2009
2. Molecular I de M, IMM. IMM Scientific Report [Internet]. Instituto de Medicina Molecular; 2014. Available from: https://imm.medicina.ulisboa.pt/files/5914/3948/2633/IMM_Scientific_Report_2014.pdf
3. Molecular I de M. Joaquim Ferreira Lab [Internet]. Vol. 2016. Instituto de Medicina Molecular; Available from: https://imm.medicina.ulisboa.pt/pt/investigacao/laboratorios/ferreira-lab/
4. NOTE FOR GUIDANCE ON DEFINITIONS AND STANDARDS FOR EXPEDITED REPORTING [Internet]. Vol. 2016. 2004. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002807.pdf
5. Agency EM. European Medicines Agency. 2013;(October 2003). Available from: http://en.wikipedia.org/wiki/European_Medicines_Agency#cite_note-1
6. Jackson NC. Unit One: Background to Systematic Reviews. Cochrane Handb - Syst Rev Heal Promot public Heal Interv [Internet]. 2004;p.1. Available from: https://ph.cochrane.org/sites/ph.cochrane.org/files/uploads/Unit_One.pdf
7. INFARMED. Lei n.º 21/2014, de 16 de abril [Internet]. INFARMED, editor. INFARMED; 2014. Available from: http://www.aprefar.pt/pdf/036-B1_Lei_21_2014.pdf
8. Griffin JP, Wiley-Blackwell. The textbook of Pharmaceutical Medicine . 6th editio. BMJ Books; 2009.
9. Bhatt A. Evolution of Clinical Research: A History Before and Beyond James Lind. Perspect Clin Res [Internet]. 2010;1(1):6–10. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3149409/
10. Organization WH. Clinical trials [Internet]. Vol. 2016. World Health Organization; Available from: http://www.who.int/topics/clinical_trials/en/
11. Services USD of H and H. Learn About Clinical Studies [Internet]. Vol. 2016. U.S.: U.S. Department of Health and Human Services; 2015. Available from: https://clinicaltrials.gov/ct2/about-studies/learn#ClinicalTrials
12. Roche. What is a clinical trial and how does a trial work? [Internet]. Vol. 2016. Roche; 2014. Available from: http://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/what_is_a_clinical_trial.htm?acc1=tab2
13. Pfizer. What Are Clinical Trials? [Internet]. Vol. 2016. Pfizer; Available from: http://www.pfizer.com/research/clinical_trials/phases_of_development
14. Authorisation Procedures for medicinal products [Internet]. Vol. 2016. 2016. Available from: http://ec.europa.eu/health/authorisation-procedures_en.htm
15. Harmonization IC on. E8 General Considerations for Clinical Trials [Internet]. International Conference on Harmonization; 1997. p. 5. Available from: http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/general-considerations-for-clinical-trials.html
16. Association WM. WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects [Internet]. Vol. 2016. World Medical Association; 1964. Available from: http://www.wma.net/en/30publications/10policies/b3/
17. Services USD of H& H. The Nuremberg Code [Internet]. Vol. 2016. U.S. Department of Health & Human Services; 2005. Available from: http://www.hhs.gov/ohrp/archive/nurcode.html
18. Department of Health and Welfare. E. The Belmont Report [Internet]. Vol. 2016.

Department of Health, Education, and Welfare.; 1979. Available from: http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html
19. Harmonisation IC on. About ICH [Internet]. Vol. 2016. International Conference on Harmonisation; Available from: http://www.ich.org/about/vision.html
20. Commission E. COMMISSION DIRECTIVE 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or im [Internet]. Commission E, editor. Vol. L 91/13, Perspectives in Clinical Research. Official Journal of the European Union; 2005. Available from: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2005_28/dir_2005_28_en.pdf
21. Commission E. COMMISSION DIRECTIVE 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use [Internet]. Commission E, editor. Vol. L 262/22. Official Journal of the European Union; 2003. Available from: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2003_94/dir_2003_94_en.pdf
22. Commission E. DIRECTIVE 95/46/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL OF 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data [Internet]. Commission E, editor. Vol. L 281/31. Official Journal of the European Union; 1995. Available from: http://ec.europa.eu/justice/policies/privacy/docs/95-46-ce/dir1995-46_part1_en.pdf
23. Commission E. Clinical trials - Regulation EU No 536/2014 [Internet]. Vol. 2016. European Commission; 2014. Available from: http://ec.europa.eu/health/human-use/clinical-trials/regulation/index_en.htm#ct1
24. Dehlinger-Kremer M. The New EU Clinical Trials Regulation: The Good, the Bad, the Ugly. SynteractHCR;
25. Union E. Regulations, Directives and other acts [Internet]. Available from: http://europa.eu/eu-law/decision-making/legal-acts/index_en.htm
26. INFARMED. Ensaios Clínicos [Internet]. Vol. 2016. INFARMED; Available from: http://www.infarmed.pt/portal/page/portal/INFARMED/MEDICAMENTOS_USO_HUMANO/ENSAIOS_CLINICOS
27. ClinicalTrials.Gov. Trends, Charts, and Maps [Internet]. Vol. 2016. ClinicalTrials.Gov; 2015. Available from: https://clinicaltrials.gov/ct2/resources/trends
28. APIFARMA, APIFARMA. Ensaios clínicos em Portugal [Internet]. APIFARMA; 2013. Available from: http://www.aibili.pt/ficheiros/EstudoInvestigClinica_em_Portugal_jun2013vf.pdf
29. EU Clinical Trials Register [Internet]. European Medicines Agency; Available from: https://www.clinicaltrialsregister.eu/ctr-search/search
30. List of Countries by projected GDP (PPP) per capita (2015-2020) [Internet]. Vol. 2016. 2015. Available from: http://statisticstimes.com/economy/countries-by-projected-gdp-capita-ppp.php
31. INFARMED. Statistics of Clinical Trials Assessed by Infarmed - Annual evolution 2005 - 2015 [Internet]. Vol. 2016. INFARMED; Available from: http://www.infarmed.pt/portal/page/portal/INFARMED/MEDICAMENTOS_USO_HUMANO/ENSAIOS_CLINICOS/ESTATISTICAS/UEC_ENGLISH_VERSION
32. RONALD D. MANN EBA, Wiley. PHARMACOVIGILANCE. Wiley; 2007.
33. Commission E. The EU pharmacovigilance system [Internet]. Vol. 2016. European Commission; Available from: http://ec.europa.eu/health/human-use/pharmacovigilance/index_en.htm
34. INFARMED. Farmacovigilância dos Ensaios Clínicos [Internet]. Vol. 2016. INFARMED; Available from: http://www.infarmed.pt/portal/page/portal/INFARMED/MEDICAMENTOS_USO_HUMANO/FARMACOVIGILANCIA/FARMACOVIGILANCIA_ENSAIOS_CLINICOS

35. Pharmacovigilance legislation [Internet]. Vol. 2016. European Medicines Agency; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000491.jsp&mi
36. Commission E. DIRECTIVE 2012/26/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 25 October 2012 amending Directive 2001/83/EC as regards pharmacovigilance [Internet]. Vol. L 299/1. Official Journal of the European Union; 2012. Available from: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:299:0001:0004:EN:PDF
37. Commission E. DIRECTIVE 2011/62/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 8 June 2011 [Internet]. Commission E, editor. Vol. L 174/74. Official Journal of the European Union ; 2011. Available from: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2011_62/dir_2011_62_en.pdf
38. INFARMED. Legislação de Farmacovigilância e documentos publicados pela EMA [Internet]. Vol. 2016. INFARMED; Available from: http://www.infarmed.pt/portal/page/portal/INFARMED/MEDICAMENTOS_USO_HUMANO/FARMACOVIGILANCIA/NOVA_LEGISLACAO_FARMACOVIGILANCIA
39. Commission E. REGULATION (EU) No 1027/2012 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 25 October 2012 amending Regulation (EC) No 726/2004 as regards pharmacovigilance [Internet]. Council EP and of the, editor. Vol. L 316/38. Official Journal of the European Union ; 2012. Available from: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:316:0038:0040:EN:PDF
40. Commission E. COMMISSION IMPLEMENTING REGULATION (EU) No 520/2012 of 19 June 2012 [Internet]. Commission E, editor. Vol. L 159/5. Official Journal of the European Union ; 2012. Available from: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:159:0005:0025:EN:PDF
41. Herdeiro MT, Ferreira M, Ribeiro-Vaz I, Junqueira Polonia J, Costa-Pereira A. [The Portuguese Pharmacovigilance System]. Acta Med Port. 2012/10/20 ed. 2012;25(4):241–9.
42. Krishnankutty B, Bellary S, Kumar NBR, Moodahadu LS. Data management in clinical research: An overview. Indian J Pharmacol [Internet]. 2012;44(2):168–72. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3326906/
43. Sharma S. How to Become a Competent Medical Writer? Perspect Clin Res [Internet]. 2010;1(1):33–7. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3149406/
44. Gonçalves S. Interações entre o investigador e o promotor (visita de pré-estudo, seleçãodo investigador, orçamento e contrato, visita de iniciação). CLIC;
45. Clinicaltrialsregister.eu. Clinical trials for WA25046 [Internet]. Clinicaltrialsregister.eu; Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=wa25046
46. Clinicaltrialregister.eu. Clinical Trials - BAF312 [Internet]. Clinicaltrialregister.eu; Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2012-003056-36/PT
47. Clinicaltrialregister.eu. Clinical trials [Internet]. Clinicaltrialsregister.eu; Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2013-001656-35/PT
48. ClinicalTrials.Gov. Study Record Detail [Internet]. U.S National Institutes of Health ; Available from: https://clinicaltrials.gov/ct2/show/NCT01590589?term=registry&rank=5